12-2001

Methodology developed during the synthesis of a truncated analog of hydramycin

David C. White
University of Tennessee

To the Graduate Council:

I am submitting herewith a dissertation written by David C. White entitled "Methodology developed during the synthesis of a truncated analog of hydramycin." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

David C. Baker, Major Professor

We have read this dissertation and recommend its acceptance:

Jeffery Becker, Ziling Xue, David Young

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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Methodology Developed During the Synthesis of a Truncated Analog of Hydramycin

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

David C. White
December 2001

DEDICATION

This dissertation is dedicated to all the

men, women and children who lost their lives

in the wreckage of September 11, 2001

and

to the Heros who emerged from the rubble.

–Their memory and spirit are the inspiration of a nation–

ACKNOWLEDGMENTS

The author expresses his deepest thanks and sincere appreciation to Dr. David C. Baker for his continuous support and limitless patience. It was a privilege to develop into a professional chemist under his guidance. His advice, knowledge, and stories will always be remembered.

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The author would like to express his appreciation for the collaborative efforts and contributions of Sarah Sanzenbacher to the hydramycin project. Together Sarah and the author designed and executed everything in this project—an effort they can call their own. In addition, he wants to thank those members of the Baker Group that aided him during his tenure there by: giving their friendship, sharing their experiences and knowledge in chemistry and teaching him true patience (whether intentional or not).

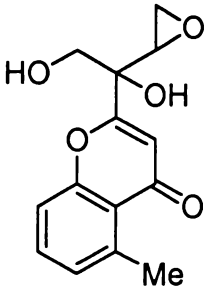
The author would like to thank his family, both current and to be, for their encouragement, love and patience. They gave him a reason to strive to succeed

and enjoy every moment of life.

Most importantly, the author wants to thank God for the talents and the skills that He provided the author to use in his search for new discoveries in organic chemistry and shaping him into the man he is now.

ABSTRACT

Several unique strategies were developed and employed in the synthesis of 2-(1,2-dihydroxy-1-oxiranylethyl)-5-methylchromen-4-one (**1**) during a model study for the synthesis of hydramycin (**2**)—an antitumor antibiotic. Hydramycin, a pyranoanthraquinone, was isolated from a strain of *Streptomyces* and shown to exhibit both cytotoxic and antibiotic properties. This dissertation will cover the



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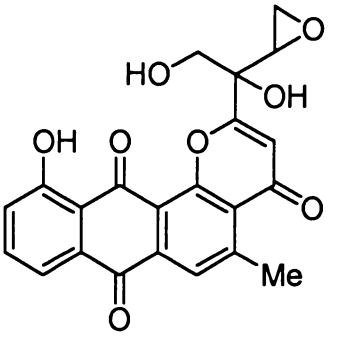

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developments, challenges and solutions discovered in the total synthesis of truncated analog **1**, which contains the functionality found in **2**, and the methodology to generate an anthraquinone system that could be used for the ultimate synthesis of **2**.

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

°C	degrees Celsius
µmol	micromoles
9-BBN	9-borabicyclo[3.3.1]nonane
$AlCl_3$	aluminum trichloride
Br_2	bromine
CaH_2	calcium hydride
$CaSO_4$	calcium sulfate
CBr_4	carbon tetrabromide
CCl_4	carbon tetrachloride
$CDCl_3$	chloroform-*d*
CDI	1,1'-carbonyldiimidazole
CH_2Cl_2	methylene chloride
CH_3CN	acetonitrile
$CHCl_3$	chloroform
DIPEA	diisopropylethylamine
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	dimethyl-d_6 sulfoxide
Et_3N	triethylamine
$FeCl_3$	ferrous(III) chloride
g	grams
h	hours
H_2O_2	hydrogen peroxide
H_2SO_4	sulfuric acid
HBr	hydrobromic acid

HCl	hydrochloric acid
HFA	Hollow Fiber Assay
HOAc	acetic acid
Hz	hertz
IR	infrared
K_2CO_3	potassium carbonate
$K_2S_2O_8$	potassium persulfate
KBr	potassium bromide
KF	potassium fluoride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
M	molarity (moles per liter)
m-CPBA	*m*-chloroperoxybenzoic acid
Me_2SO_4	dimethyl sulfate
MeI	iodomethane
MeLi	methyl lithium
MEMCl	methoxyethoxymethyl chloride
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimoles
MnO_2	manganese(IV) dioxide
mol	moles
MPMCl	*p*-methoxybenzyl chloride
MsCl	mesityl chloride
n-BuLi	*n*-butyl lithium

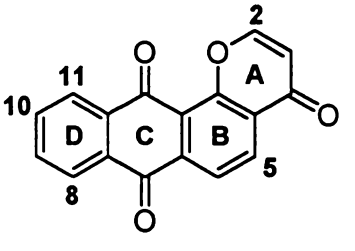
Na_2CO_3	sodium carbonate
$Na_2S_2O_3$	sodium thiosulfate
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride
NaCl	sodium chloride
$NaClO_2$	sodium chlorite
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
$NaIO_4$	sodium periodate
NaOH	sodium hydroxide
NBS	*N*-bromosuccimide
NH_4Cl	ammonium chloride
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
$POCl_3$	phosphorus oxychloride
RT	room temperature
SeO_2	selenium dioxide
TBAF	tetrabutylammonium fluoride
TBSCl	*tert*-butylchlorodimethylsilane
TESCl	chlorotriethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilane
uv	ultraviolet

I. BACKGROUND

A. Introduction

Natural products research is continuously discovering compounds that exhibit biological and pharmacological activity, including antibiotic and cytotoxic activity. The discovery of numerous compounds that can be subjected to quick preliminary screening for biological activity has led to a surge in the isolation of potent candidates that can undergo more detailed activity studies. Along with a thorough pharmacophoric assessment, these detailed studies lead to complete structural determination which gives rise to structure–activity relationships (SAR). Since these isolated drug candidates have origins in biosynthesis, the development of suitable synthetic pathways proves to be a difficult yet crucial step towards the task of generating a marketable drug for cancer chemotherapy or antibiotic treatment.

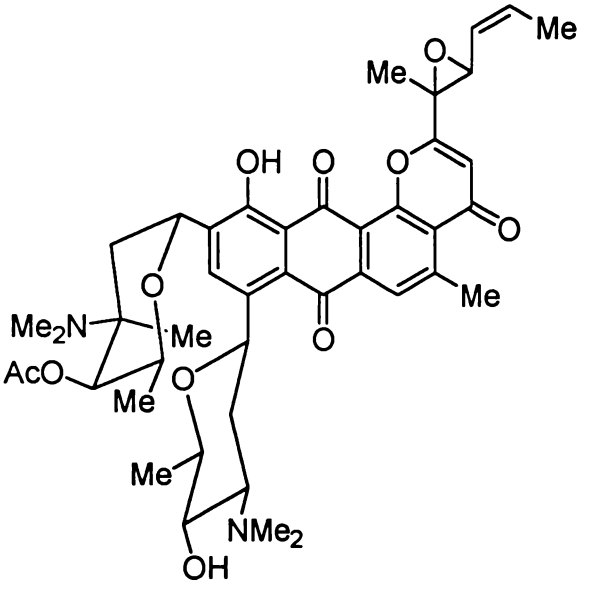
Much interest has been focused on the biological activity of pyranoanthraquinones—a class of compounds consisting of an anthraquinone



pyranoanthraquinone

ring skeleton (rings B,C and D) fused to a γ-pyranone ring (ring A). Substituents vary greatly among known pyranoanthraquinones; however, compounds that

contain some or all of the following groups attract much attention: a methyl group at C5, a mutli-functionalized alkyl chain at C2 with an epoxide subunit, sugar moieties (especially at C8 and C10) and a hydroxy group at C11.[1] When containing sugar rings, these pyranoanthraquinones are also referred to as pluramycins,[2] or anthra[1,2-*b*]pyran antibiotics;[3,4] however, when no sugar system is present they are referred to as pluramycinones.[5] From structure–bioactivity studies of pyranoanthraquinones, it was discovered that the epoxide subunit is critical. The epoxide serves as a site of nucleophilic attack by guanine N7 in duplex DNA. This covalent bonding results in effective DNA alkylation.[6-9] These 4*H*-anthra[1,2-*b*]pyran-4,7,12-triones have been studied for antitumor and antimicrobial activity since the isolation and discovery of the first

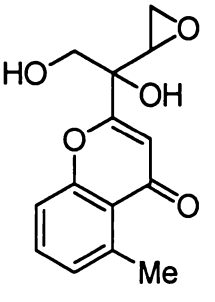


Pluramycin A **SF-2330**

bioactive pluramycin (pluramycin A) in 1956 from *Streptomyces pluricolorescens*[5,10] and the first pluramycinone (SF-2330) in 1986 from

Streptomyces sp. SF-2330.[11,12]

In 1991, one such potent pluramycinone was isolated from the fermentation broth of *Streptomyces violaceus* P950-4 (ATCC 53807) from a soil sample collected in Hyderabad, Andhra Pradesh State, India.[13] The recovered compound, hydramycin (**2**)—11-hydroxy-5-methyl-4*H*-anthra[1,2-*b*]pyran-4,7,12-trione—not only displayed strong antibacterial activity against Gram-positive



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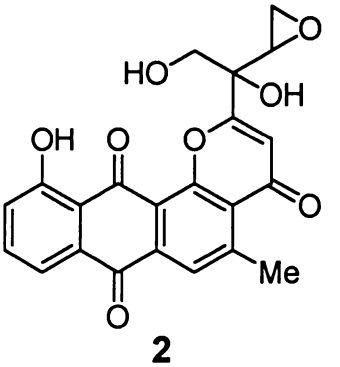

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bacteria, but showed potent cytotoxicity activity. In 1992, a screening run by the National Cancer Institute (NCI) indicated potent antitumor activity against prostate cancer with an HFA value of 16.[14,15] Because of the inherent pharmacological activity in hydramycin and the potential for the study of the SAR of pluramycinones, a total synthesis seemed prudent.

B. Outline of Employed Synthetic Strategies

Through retrosynthetic analysis of hydramycin (Scheme 1), it was possible to envision two unique disconnections rendering two synthons: an anthraquinone moiety and a functionalized side chain. These two synthons could be cyclized in some manner to establish the pyranone ring system. There were several very

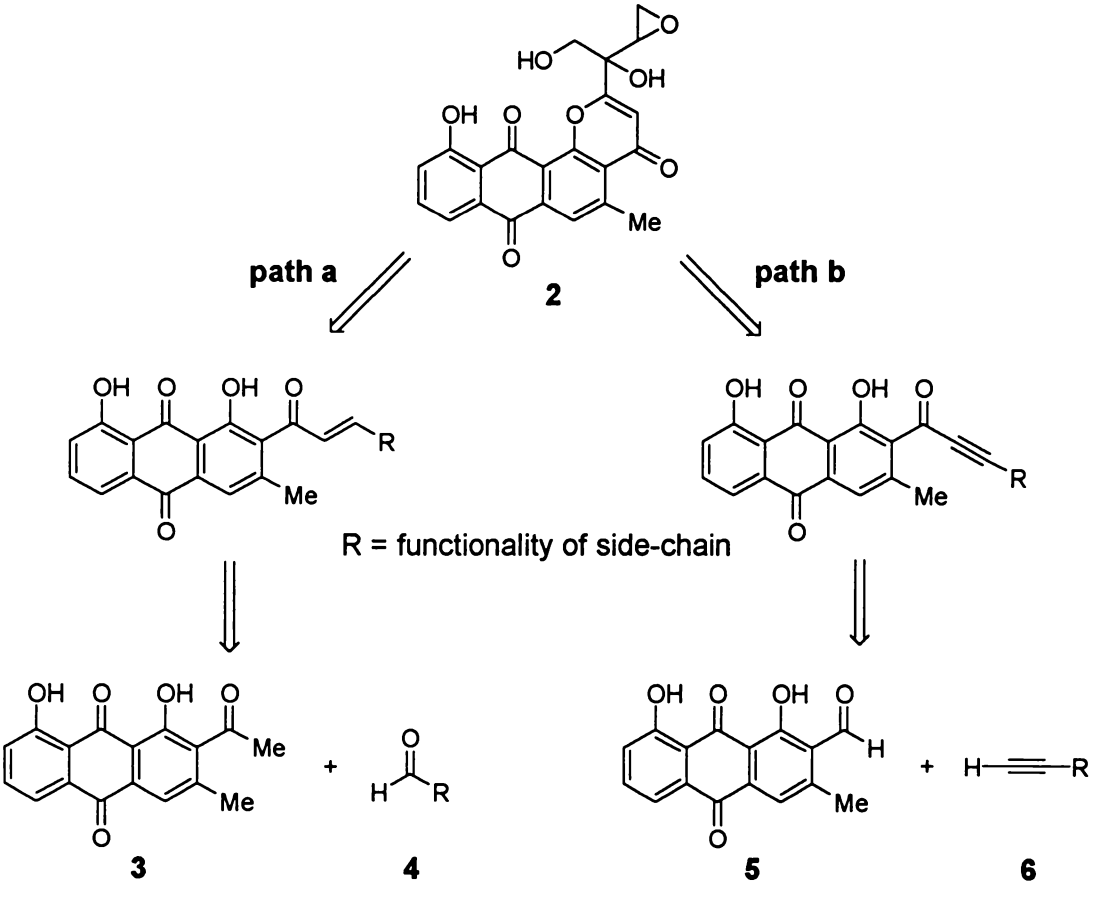
different approaches explored during the synthesis of these two synthons. These will be discussed in two categories—methods involving aldol chemistry and methods involving alkynyl coupling—each with several variations.

1. Aldol Condensation Methods

One pathway for the synthesis of hydramycin (Scheme 1, path a) would require an anthraquinone moiety containing an acetyl group at C2, which through aldol chemistry with an appropriate aldehyde could generate an α,β-unsaturated system that could be cyclized into a pyranone ring. The appropriate functionality on the alkyl side chain could either be installed on the aldehyde synthon before the aldol reaction or after. Both possibilities will be discussed in this dissertation.

Generation of the side chain **4** for an aldol reaction appeared to offer the most challenges. A decision on whether to install the functionality on the side chain before the condensation or add the functionality afterwards was needed (Scheme 2). If aldehyde **7** was condensed with an aromatic compound followed by cyclization, then the olefins could provide a platform for a dihydroxylation and an epoxidation to provide the functionality of **1**. Conversely, use of aldehyde **8** would allow the hydroxyl and epoxide group to be installed prior to condensation and cyclization.

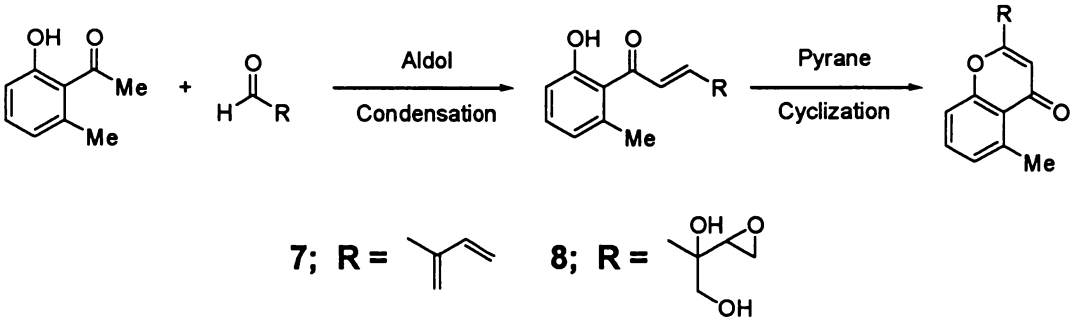
For a total synthesis of hydramycin, the anthraquinone system **3** must be prepared. In 1980, Hauser and Rhee[3] outlined a total synthesis of *O*-methylkidamycinone, a pluramycinone without the apparently necessary epoxide subunit using SeO_2 to cyclize the pyranone ring. An attempt made to fashion a



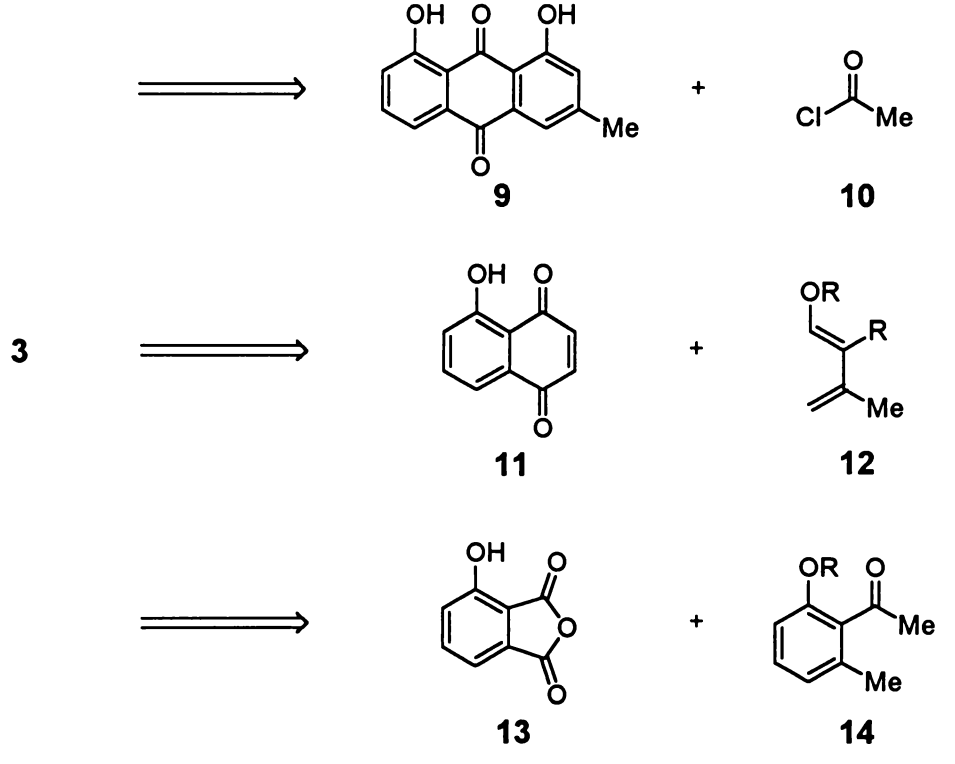
Scheme 1. Retrosynthetic Analysis of Hydramycin

synthetic scheme for hydramycin from Hauser's work yielded a non-convergent method with 24 steps. Attention was turned to developing a more convergent method that still used an aldol condensation for coupling. Focusing on the anthraquinone moiety **3** (Scheme 1, path a), there were several viable theories on its synthesis (Scheme 3). First, a Friedel–Crafts reaction between 1,8-dihydro-3-methylanthraquinone (chrysophanic acid, **9**), which is commercially available or could be synthesized, and acetyl chloride (**10**) could directly provide the desired anthraquinone **3**. Second, a Diels-Alder reaction between 3-hydroxyjuglone (**11**) and a properly functionalized diene (**12**), followed by aromatization, could generate the anthraquinone **3**. Third, a reaction involving the Friedel–Crafts coupling of 3-hydroxyphthalic anhydride (**13**) with an acetophenone analog (**14**) might synthesize **3**. Finally, **3** could be generated using the method developed from the *O*-kidamycinone synthesis; however, the desired convergency would be lost (Scheme 4). In a study of 9,10-dihydro-4,5-dihydroxy-3-malonamoyl-9,10-dioxo-2-anthraceneacetic acid (protetrone), a synthesis of **3** was reported; however, the original starting material was isolated in a metabolic biosynthesis, so this option was not explored further.[16]

Using the methodology discovered in the model studies of the aldehyde side chain synthon and the synthesis of anthraquinone **3**, the hope was to develop a total synthesis of analog **1**, which could lead to the eventual synthesis of **2**. Methods utilizing the aforementioned aldol chemistry will be discussed later in this dissertation.



Scheme 2. Possible Aldol Condensation Reactions

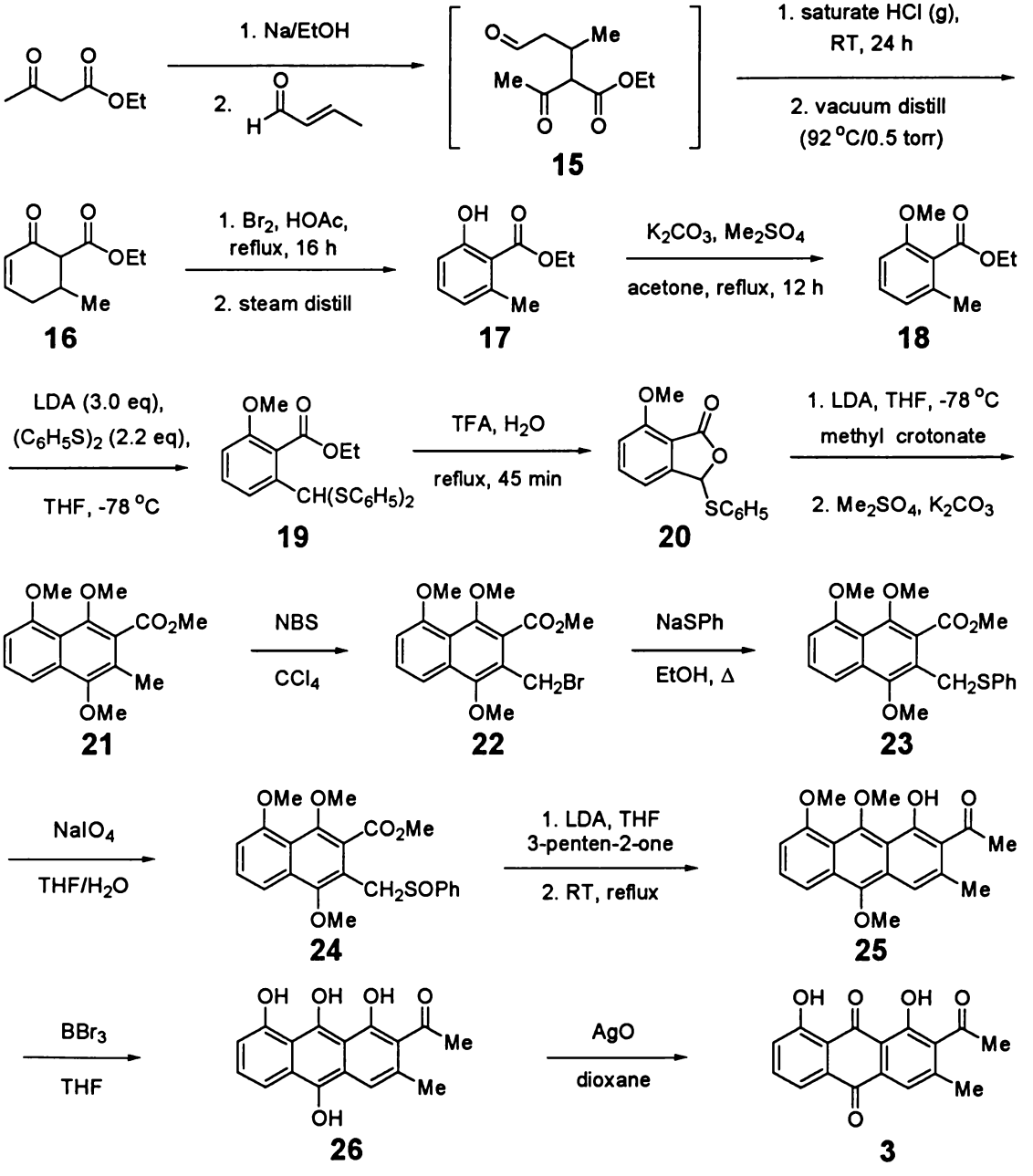


Scheme 3. Retrosynthetic Analysis of Anthraquinone **3**

2. Alkynyl Coupling Methods

Another pathway (Scheme 1, path b) for the total synthesis of hydramycin that was explored involved the coupling of an aldehyde at C2 of the anthraquinone system **5** with an alkynyl side chain synthon (**6**). After oxidation of the coupled product, pyranone ring formation could be achieved by 6-*endo-digonal* closure.[17] Previously reported research on pyranoanthraquinone analogs suggests that if an appropriate alkyne could be generated, it would be possible to couple with an anthraquinone aldehyde followed by fluoride-induced pyranone ring closure to generate hydramycin.[1,6-8] Another procedure using alkynyl chemistry was reported for the synthesis of pyranoanthraquinones;[18-20] however, this method could not be taken advantage of because of the coupling procedure.

The alkynyl side chain synthon appeared to show the greatest signs of difficulty for synthesis, since the functionality had to survive the coupling conditions, or be installed afterwards (Scheme 5). Through the coupling of a substituted benzaldehyde (**27**) with the organometallic salt of an alkyne **6** and oxidation of the resulting alcohol could give an ethynyl ketone (**28**). Keto-compound **28** could be cyclized into the needed pyranone compound (**29**) and elaborated. This methodology could be employed using anthraquinone **5** leading to the synthesis of **2**. Attention was given to a model study that could test both the proposed chemistry and generate an analog that could possibly aid in better understanding the SAR of **1**. The pluramycinones contain an anthraquinone moiety; however, several studies have shown that the epoxide subunit off the alkyl chain on C2 is responsible for much of the biological activity, therefore the

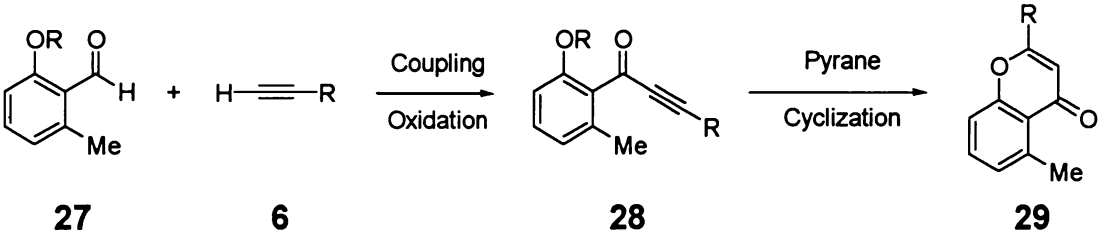


Scheme 4. Non-convergent Synthesis of Anthraquinone **3**

anthraquinone ring system might not be necessary.[8]

C. Dissertation Overview

This dissertation will cover the developments, challenges and solutions discovered in the total synthesis of 2-(1,2-dihydro-1-oxiranylethyl)-5-methylchromen-4-one (**1**) and an appropriate anthraquinone synthon for future elaboration into **2**. The methodology developed for the synthesis of truncated analog **1** could be adapted into a total synthesis of hydramycin.



27 **6** **28** **29**

Scheme 5. Alkynyl Coupling and Cyclization for Pyranone Synthesis

II. STATEMENT OF THE PROBLEM

A few syntheses exist for generating pluramycinones; however, these methods are long and designed specifically for individual structures. In addition these structures contain complicated functionality, which can be difficult to synthesize. The research goal was to develop a convergent synthetic strategy that installed all appropriate functionality onto an appropriate moiety. Therefore, this dissertation will delve into the synthetic strategies employed in the generation of a truncated analog (**1**) of hydramycin. This abbreviated analog contains the pyranone ring system and functionality of **2**. The synthesis of an appropriate anthraquinone system will also be explored in this dissertation. The synthetic route developed could be expanded to include the full anthraquinone ring moiety, yielding **2** and possibly other pluramycinones.

III. DISCUSSION

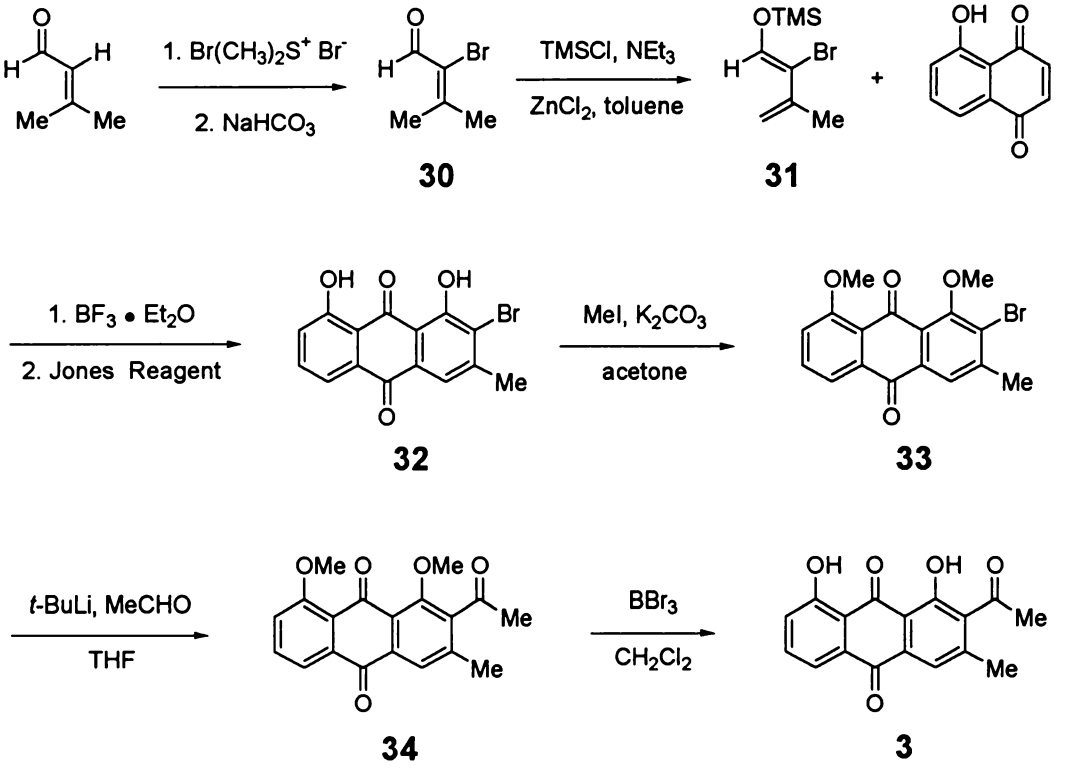
A. Anthraquinone Synthesis

For the synthesis of pluramycinone analogs, there arises the need for properly functionalized anthraquinones. Synthesis of anthraquinones **3** and **5** are essential for utilizing both the aldol and alkynyl chemistry. The developments, complications and techniques explored during the development of these anthraquinones is discussed below.

1. Diels–Alder Approach Towards Anthraquinone Synthon 3

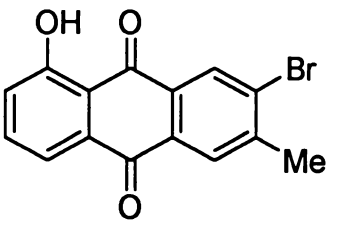
There have been reports of anthraquinone synthesis utilizing Diels–Alder chemistry;[21] therefore, such an approach for the synthesis of the anthraquinone synthon **3** was envisioned (Scheme 6). After preparing a Danishefsky-like diene[22,23] (**31**), it could be coupled to 5-hydroxy-1,4-quinone (juglone).[24-26] After oxidative aromatization of the Diels–Alder product, protection of 1,8-dihydroxyanthraquinone as the methyl ether could be achieved with MeI and K_2CO_3. A lithium halide exchange and subsequent reaction with acetaldehyde, followed by *O*-demethylation, would lead to the desired anthraquinone **3**.

Through the use of bromodimethylsulfonium bromide, it was possible to generate the α-bromo compound **30** from acrolein.[27] This was accomplished by generation of the electrophilic reagent from dimethyl sulfide and Br_2 in CH_3CN at low temperature. When added to an α,β-unsaturated carbonyl compound, such as acrolein, the electrophile adds to the unsaturation furnishing an α-bromo-β-



Scheme 6. Diels–Alder Approach to the Synthesis of Anthraquinone **3**

dimethylsulfonium carbonyl compound. This compound can be subjected to aqueous $NaHCO_3$ conditions that facilitate the elimination of the α-proton, with subsequent expulsion of dimethyl suflide, leaving the desired α-bromo compound **30**. Reaction of **30** with TMSCl in the presence of Et_3N led to the generation of the trimethylsilyl enol ether **31**.[28,29]



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The hope was to use either a catalyzed or uncatalyzed Diels–Alder reaction, followed by oxidative aromatization, to generate anthraquinone **3**. It was discovered that when diene **31** was reacted with juglone, followed by subsequent treatment with Jones reagent, the desired anthraquinone was not achieved. Instead, the anthraquinone **35** was isolated. The Diels–Alder reaction was performed under varying conditions: boron trifluoride ethyl etherate and $AlCl_3$ as catalysts, as well as with no catalyst. The temperature and reaction times were altered; however, these variations only lead to different yields of the same anthraquinone **35**. It was concluded that during the aromatization reaction expulsion of the trimethylsilyloxy ether occurred. This proved to be a major setback, since the hydroxyl group is essential for the closing of the pyranone ring to generate the full pluramycinone ring system.

2. Synthesis of Anthraquinone 3 via a Procedure Based on *O*-Methylkidamycinone

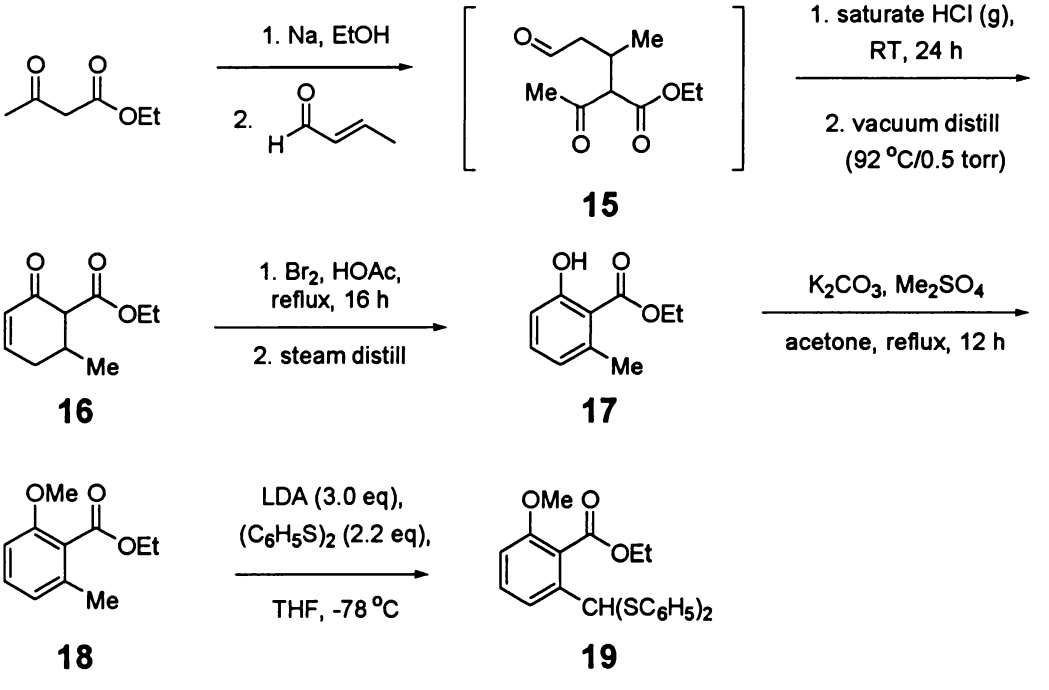
As stated earlier, the potential existed to synthesize anthraquinone **3** by a procedure based upon the synthesis of *O*-methylkidamycinone (Scheme 4).[3] If

successful, this procedure to generate **3** would prove to be a total of fifteen steps. The goal of this dissertation research was to develop methodology that could lead or would give a total synthesis of hydramycin that would be concise and convergent. This method lacked both; however, it was pursued as a last recourse concurrently with other methods (Scheme 7).

By a sodium ethoxide-catalyzed condensation of ethyl acetoacetate and crotonaldehyde, intermediate **15** was generated. Without isolation, this intermediate was treated with HCl (g) to induce intramolecular cyclization into cyclohexanone **16**. Addition of Br_2 in HOAc and CCl_4 was used to initiate aromatization of **16** into ethyl 2-hydroxy-6-methylbenzoate (**18**), which could be *O*-methylated with Me_2SO_4. The resulting toluate **18**, upon reaction with 3 equivalents of LDA and 2.2 equivalents of phenyl disulfide yielded **19**. This method, which was pursued through five steps, was aborted due to the length of the method and changes made during the dissertation research.

3. Molten Salt Friedel–Crafts Reaction

To avoid the troubles of the Diels–Alder reaction and the laborious process based upon *O*-methylkidamycinone, the concept of constructing the anthraquinone ring system through a Friedel–Crafts reaction was adopted. Through the use of molten salt chemistry, the desired anthraquinone could possibly be synthesized. During the synthesis of some aminated naphthacenetriones,[30] the Friedel–Crafts coupling of phthalic anhydride to 2,3-dimethylphenol was achieved by utilizing a molten mixture of $AlCl_3$ and NaCl.

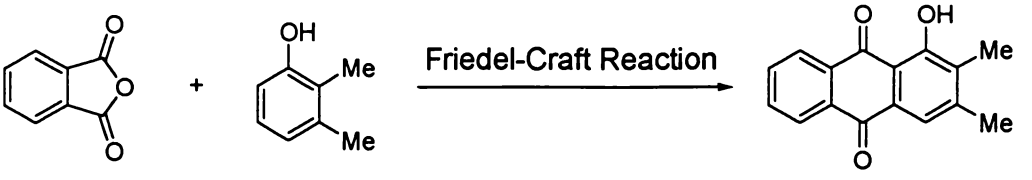


Scheme 7. Synthesis of Ethyl 2-(Bis-phenylsulfanylmethyl)-6-methoxybenzoate

Similar conditions were employed during studies of the herb *Hedyotis diffusa*[31] and synthetic strategies of kermesic acid[32] and 4-demethoxydaunomycinone[33,34]—all containing the anthraquinone moiety. The reaction conditions were extremely moisture sensitive, so care had to be taken during the experimental preparation.

Initially, the hope was to perform a molten salt reaction on both phthalic anhydride and 3-hydroxyphthalic anhydride with 2,3-dimethylphenol to test the regiochemistry of the reaction (Scheme 8). If the desired anthraquinone regioisomers **36** and **37** were obtained, the 2,3-dimethylphenol could be replaced by one of several prepared aromatic derivatives (Scheme 9): 2-methoxy-6-methylbenzaldehyde (**38**), 1-(2-methoxy-6-methylphenyl)ethanol (**39**) and 2-methoxy-6-methylacetophenone (**40**). These derivatives could lead to or give the desired anthraquinone **3**.

Preparation of the aromatic derivatives began with 2,3-dimethylanisole. The peroxydisulfate ion ($S_2O_8^{-2}$) is a tremendous oxidizing agent.[35] A regiospecific oxidation of 2,3-dimethylanisole to 2-methoxy-6-methylbenzaldehyde (**38**) is possible when reacted with three equivalents of $K_2S_2O_8$, along with copper sulfate, in a 1:1 CH_3CN–water mixture.[36] Reaction of **38** with MeLi yields **39**, which can be easily oxidized to **40**. While the correct anthraquinone regioisomers **36** and **37** were indeed obtained when 2,3-dimethylphenol was used, the Friedel–Crafts coupling of the other aromatic derivatives was unsuccessful. This could be due to the electronic effects of the substituents, so other aromatics were tested including: *m*-cresol, 2,3-catechol,



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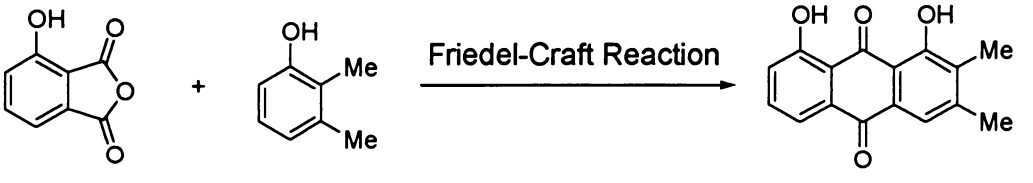

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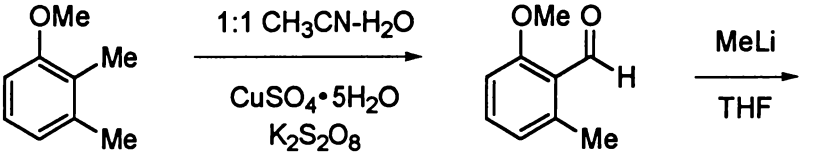
Scheme 8. Test of Regioselectivity of Molten Salt Reaction



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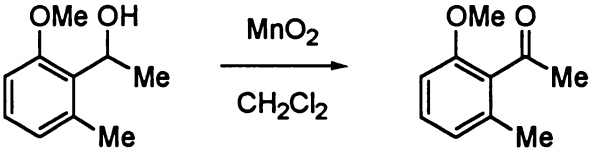
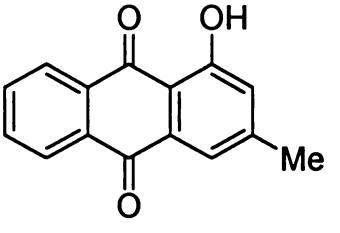


39 **40**

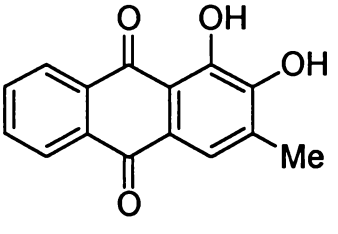
Scheme 9. Synthesis of 2-Methoxy-6-methylacetophenone

along with compounds **17** and **18**. To further test the molten salt chemistry and the role of electronics on the reaction, other aromatics were synthesized for testing (Scheme 10).

Through a Wittig reaction of **38** with *n*-BuLi and methyltriphenylphosphonium bromide, it was possible to generate 3-methyl-2-vinylanisole (**41**).[37,38] Sodium borohydride reduction of **38** led to (2-methoxy-6-methylphenyl)methanol (**42**), which upon *O*-methylation with Me_2SO_4, generated 2-methoxymethyl-3-methylanisole (**43**). Generation of 2-methoxy-6-methylbenzoic acid (**44**) was achieved from the oxidation of **38** with $NaClO_2$ and H_2O_2.[39] The *m*-cresol and 2,3-catechol reactions yielded the predicted anthraquinone products (1-hydroxy-3-methylanthraquinone and 1,2-dihydroxy-3-methylanthraquinone) and the coupling of phthalic anhydride and **44** was

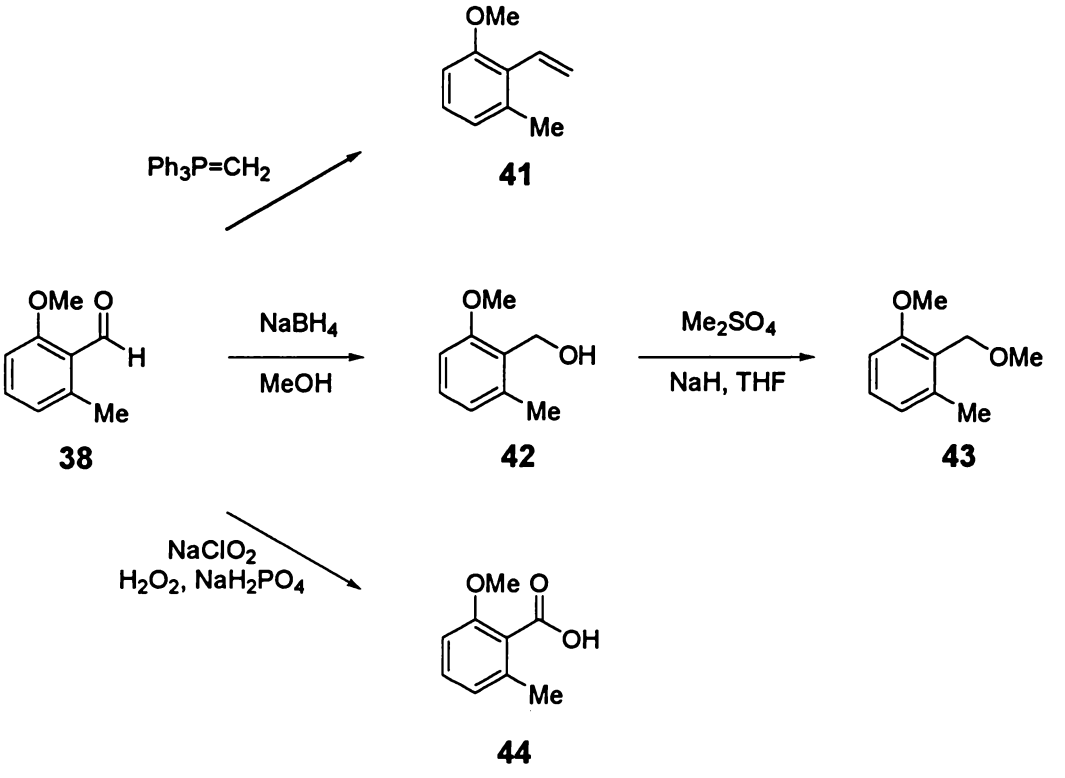


1-Hydroxy-3-methylanthraquinone

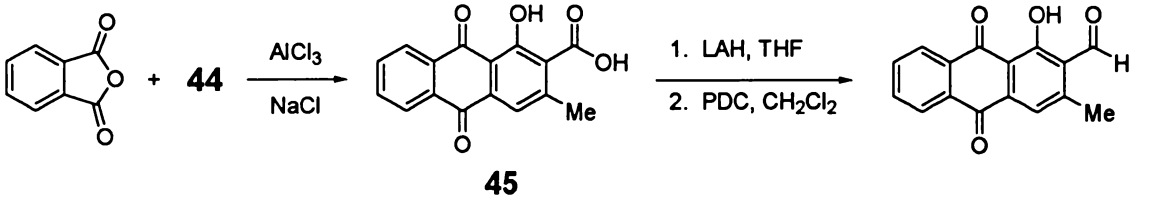


1,2-Dihydroxy-3-methylanthraquinone

successful in generating 1-hydroxy-3-methylanthraquinone-2-carboxylic acid (**45**), which upon subsequent reduction with LAH and selective oxidation yielded



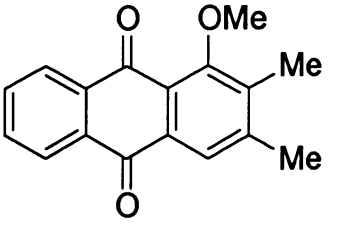
Scheme 10. Synthesis of Aromatic Derivatives of 2-Methoxy-6-methylbenzaldehye



Scheme 11. Synthesis of 1-Hydroxy-3-methylanthraquinone-2-carbaldehyde

1- hydroxy-3-methylanthraquinone-2-carbaldehyde (Scheme 11).

Another attempt to generate anthraquinone **5** was tried by O-methylation of **36** with methyl iodide and K_2CO_3 to the corresponding methyl ether, 2,3-dimethyl-1-methoxyanthraquinone (**46**). The selective oxidation procedure utilizing peroxysulfate ion was attempted on **46**. From extensive experience with the reaction, it was known that the solvent system is critical to the success of the reaction. Since the solubility of **46** was quite low in a 1:1 CH_3CN–water mixture, several approaches were tried to aid the reaction: the addition of a organic surfactant, addition of a trace amount of CH_2Cl_2 and/or toluene for solubility and the addition of pyridine, which promotes the oxidation in some cases. However, the oxidation did not occur and starting material was recovered.



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4. Overview

From the strategies explored into the synthesis of appropriate anthraquinone ring systems, it was determined that the Friedel–Crafts chemistry offered the best possibility. From the synthesis of 1-hydroxy-3-methylanthraquinone-2-carbaldehyde, an avenue to expand the methodology developed during the synthesis of the truncated analog to a compound with the anthraquinone ring system. The aldehydo anthraquinone was a potential lead into a synthesis of anthraquinones **3** and **5**, which are needed for the coupling

strategies investigated: the aldol condensation and alkynyl coupling methods.

B. Synthesis of Side Chain Synthons

For the synthesis of the target molecule and hydramycin, there were two possible side chain synthons needed depending upon path a or path b of Scheme 1: one employed an aldehyde group and one used a terminal alkyne. While both groups are necessary for coupling to an aromatic moiety, the methods for coupling are very different. This chapter will delve into the chemistry behind the synthesis of aldehyde and alkyne side chain synthons.

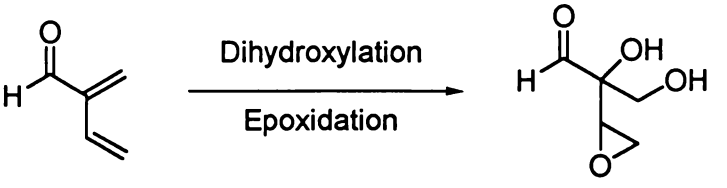
1. Aldehyde Side Chain Synthon

Several approaches were envisioned for the aldehyde side chain synthon. The aldehyde group can be reacted with an acetyl group in an aldol condensation reaction, followed by elaboration into a pyranoanthraquinone. The principal difference in methods is whether the functionality is installed before or after the aldol chemistry. Specifics of the aldol coupling chemistry will be discussed shortly.

a. Attempts to Generate a "Protected" Diene

One possible method for installing the functionality was utilizing an aldehyde with olefinic groups that could be expanded via dihydroxylation and epoxidation. Using a reported synthesis[40] of 2-acetyl-1,3-butadiene as a model,

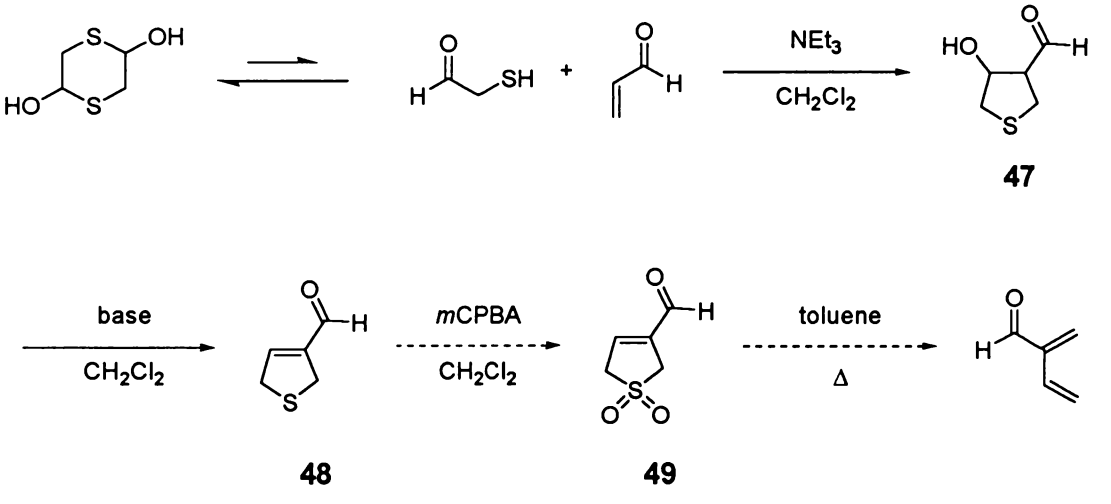
a strategy for the preparation of 2-formyl-1,3-butadiene was formed (Scheme 12). It has been shown that this diene will undergo spontaneous dimerization, so



2-Formyl-1,3-butadiene

the strategy involves leaving the diene "trapped" and coupling it through aldol chemistry to the appropriate anthraquinone **3**.

In a Michael-type reaction of 2-mercaptoethanal, which is commercially available as the dimer (*p*-dithiane-2,5-diol), along with acrolein in the presence of Et_3N, it is possible to generate the cyclic β-hydroxy compound **47**. Compound **47** can undergo catalyzed condensation forming 3-formyl-2,5-dihydrothiophene (**48**). As with the method of Belleau,[40] the β-hydroxy compound can be reacted with DIPEA and MsCl to promote the unsaturation. However, it was observed that some unsaturated product formed even without the basic workup, so the reactivity of the hydroxy group must be high. Therefore by placing **48** in dry CH_2Cl_2, along with 4Å Sieves and a catalytic amount of TFA, the condensation occurred with good yield without having to isolate **49**. Unfortunately, the oxidation of **49** into the sulfone via *m*-CPBA proved to be problematic. The hope was that, once the compound is oxidized to the sulfone and coupled to the anthraquinone, thermal extrusion of sulfur dioxide (SO_2) would generate the unprotected diene; however, the oxidation produced an inappreciable product. A concern that was present even before embarking on this strategy was the



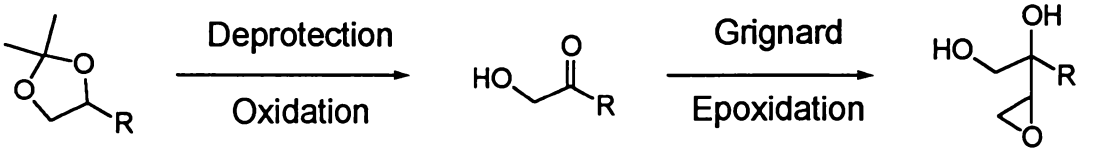
Scheme 12. Strategy for a "Protected" Diene Side Chain Synthon

stability of the final aldehyde. The corresponding 2-acetyl-1,3-butadiene will dimerize into 1,4-diacetyl-4-vinyl-cyclohex-1-ene, but it can be reacted *in situ*.[40] Other 2-substituted-1,3-butadienes undergo similar dimerization.[41,42] The proposed conclusion of the problem with the oxidation is that under the given conditions the SO_2 will thermally eliminate before use causing dimerization and/or degradation. Reports of methods for making 2-acetyl-1,3-butadiene utilizing tricarbonyliron complexes are in the literature;[43] however, this route was not explored due to the finding that the aldehyde is unstable.

b. Synthesis of Isopropylidene Glyceraldehyde

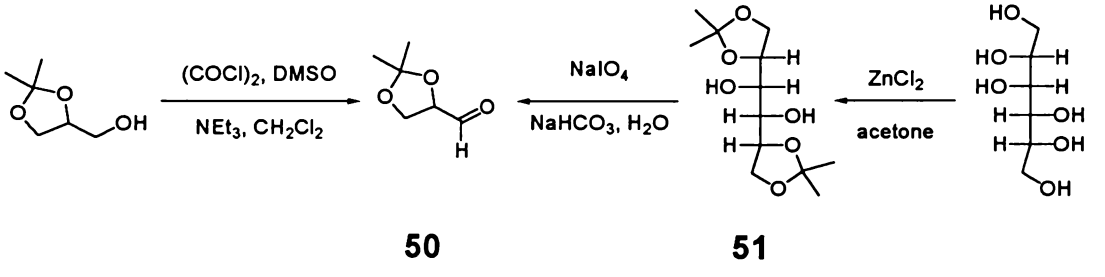
Another possibility for an aldehyde side chain synthon was to have some of the functionality installed before coupling than install the remainder afterwards. The synthon would contain the hydroxyl groups before coupling to the aromatic portion (R), then subsequent deprotection and selective oxidation would give a keto compound that could be reacted with vinylmagnesium bromide than *m*-CPBA.

The hope was to incorporate 2,3-*O*-isopropylidenegylceraldehyde (**50**) onto the anthraquinone **3** through an Aldol condensation. Several methods for the preparation of **50** were explored (Scheme 13). Oxidation of 2,2-dimethyl-1,3-dioxolane-4-methanol (solketal) was the initial premise for generation of the



aldehyde. It was reported that the oxidation of Solketal with PCC to generate **50** was unsuccessful.[44] Therefore the oxidation of Solketal using Swern conditions was contemplated; however, it was discovered that the crude product cannot be fully purified.[44-46] This may be due to the fact that an aldehyde such as **50**, that has an oxygen atom on the α-carbon can form a hydrated product, or a *gem*-diol, in the presence of water. Purification techniques cited for **50** after Swern oxidation, include distillation and silica gel column chromatography; however, when both were attempted during this research, the product degraded. Even when the crude product was subjected to silica gel TLC, the product spot had a lower R_f value than the starting alcohol. This evidence verified the hydrate phenomenon. Because of the problems with purification, a process where there was little or no post reaction cleanup would be advantageous.

The D-glyceraldehyde acetonide that is desired for the hydramycin project has been used as a chiral synthon in the synthesis of several biologically active compounds.[47] A synthetic strategy for the generation of **50** from inexpensive D-mannitol, with no significant purification problems, was employed. A comprehensive study on various isopropylidene protection methods of D-mannitol reported the best method for the synthesis of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**51**) was reacting D-mannitol with anhydrous zinc(II) chloride and dry acetone.[48] This generated the desired product and a trace amount of tri-acetonide product. The desired **51** was purified by refluxing the product in a solution of 1 mL/g of $CHCl_3$ and 10 mL/g of petroleum ether for 30 min.[49] The solution was filtered and cooled, yielding pure **51**. Oxidative cleavage of **51** with



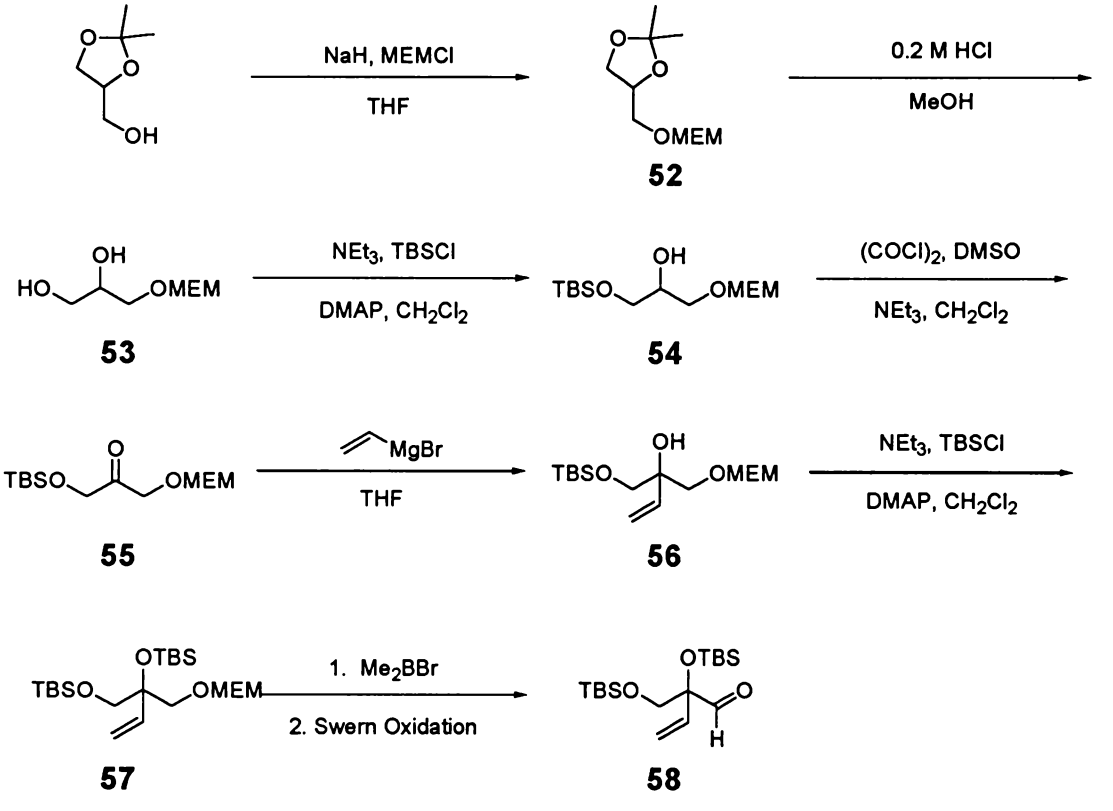
Scheme 13. Preparative Routes to Isopropylidene Glyceraldehyde

$NaIO_4$ in a 5% sodium bicarbonate media generates two equivalents of the needed aldehyde **50** with no purification.[50-52] Aldehyde **50** was collected, dissolved in a precise amount of dry THF and stored over $CaSO_4$ as a molar solution. The same cleavage can be achieved with lead tetraacetate [$Pb(OAc)_4$] in ethyl acetate.[47]

c. Functionalized Side Chain Synthons

While possibilities were explored for generation of a side chain synthon that could allow for functionality to be installed after coupling, the idea of delivering a fully functionalized side chain was also investigated. Still envisioning the use of an aldehyde for an Aldol coupling, the synthon **58**, which would contain the needed hydroxyl groups, could be brought in with protected ethers and a vinyl group present for oxidation to the oxiranyl ring. An appropriate synthetic route was formulated (Scheme 14).

Protection of Solketal with NaH and MEMCl to give the MEM ether, followed by deprotection of the *O*-isopropylidene group with 0.2 M HCl, would yield 3-(2-methoxyethoxymethoxy)-propane-1,2-diol (**53**).[53] Selective silylation of the primary hydroxyl of **53** with DMAP lends compound **54**, which upon Swern oxidation gives the keto-compound, 1-(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-propan-2-one (**55**). Reaction of **55** with vinylmagnesium bromide, then protection of the resulting alcohol **56** as the TBS ether, generates 3,4-bis-(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxymethyl)-but-1-ene (**57**). At this point, a problem arises.



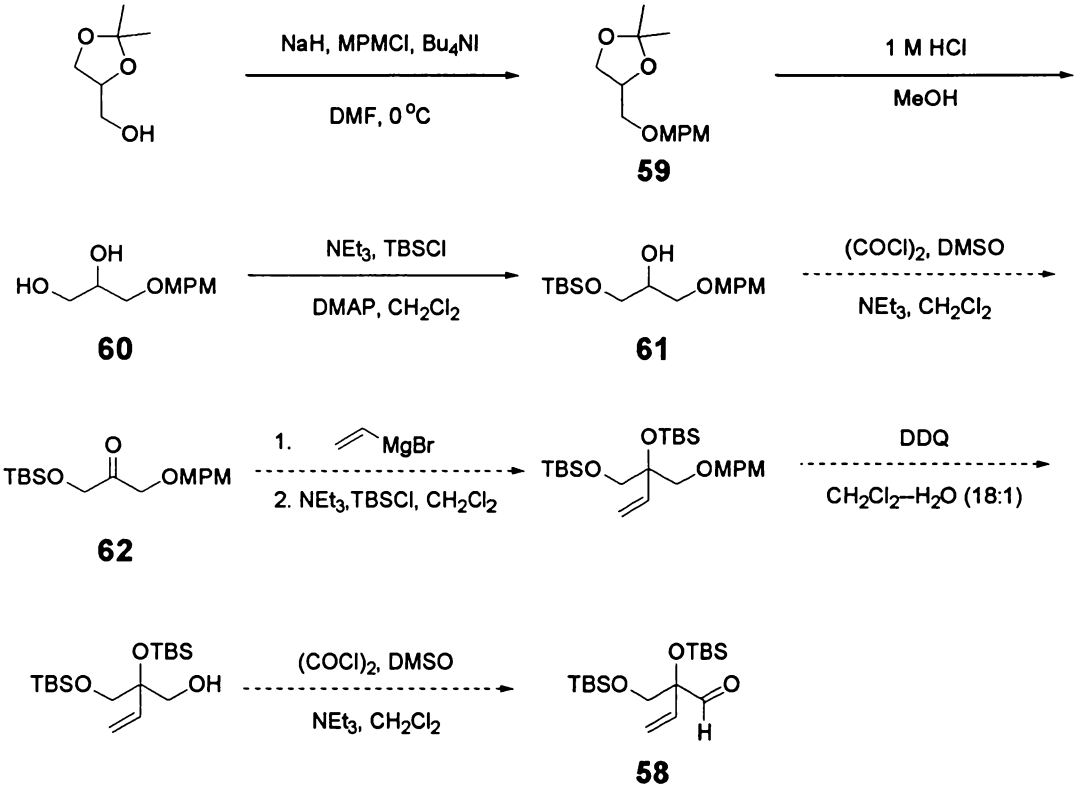
Scheme 14. Proposed Route to Functionalized Side Chain Synthon

The hope is to deprotect the MEM ether in the presence of the silyl ethers, then oxidize to the aldehyde. When attempts were made to deprotect, either small amounts of starting material were recovered or the silyl ether was removed as well. Attempts were made with dimethylboron bromide,[54] diphenylboron bromide[55] and dicyclohexylboron bromide. This problem led to the development of a route using a MPM ether instead.

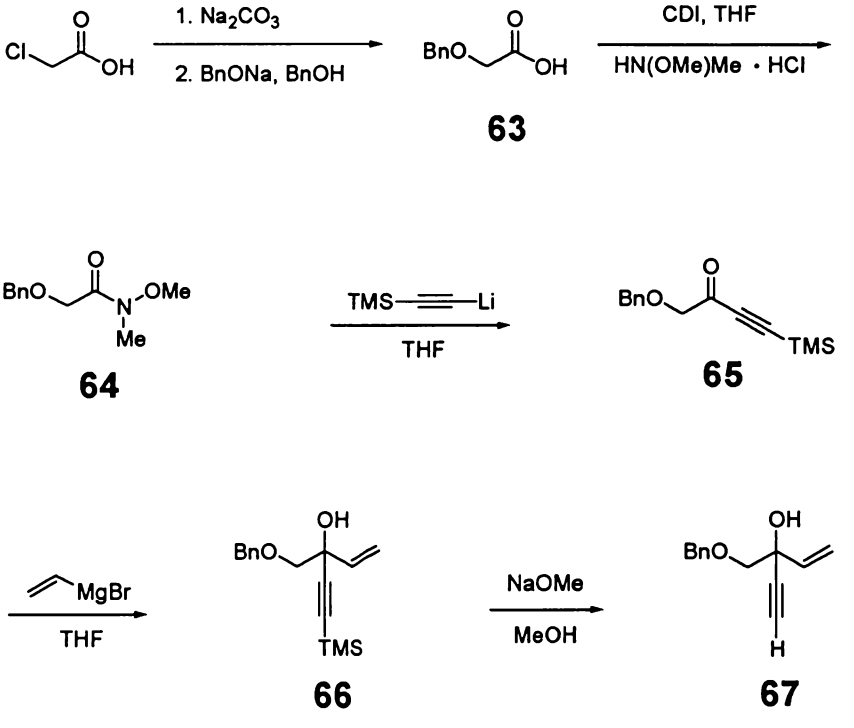
Since the MEM ether could not be successfully removed from **57**, it was replaced with a MPM ether (Scheme 15). Protection of Solketal as the MPM ether could be achieved in a similar manner as above[56,57] or with potassium *tert*-butoxide generating **59**.[58,59] With the addition of tetrabutylammonium iodide, the yield of the protection was increased. Use of a 1.0 M solution of HCl facilitated the deprotection of the *O*-isopropylidene group in **59**, yielding diol **60**.[60] The stronger acid gave a better yield then the 0.2 M solution used previously. Selective silylation gave compound **61**; however, the Aldol chemistry was abandoned, so progress on the scheme was stopped.

2. Synthesis of Alkyne Side Chain Synthon

A synthesis for an appropriately functionalized alkyne was developed (Scheme 16). Generation of benzyloxyacetic acid (**63**) was achieved by the reaction of sodium benzyloxide with the sodium salt of chloroacetic acid. Reaction of acid **63** with CDI and *N,O*-dimethylhydroxylamine hydrochloride yielded amide **64**.[61,62] The use of *N*-methoxy-*N*-methylamides, also known as Weinreb amides, as acylating agents is well known.[63] These amides are ideal for



Scheme 15. Revised Route to Functionalized Side Chain Synthon



Scheme 16. Synthesis of Alkyne Synthon: 3-Benxyloxymethyl-pent-1-en-4-yn-3-ol

controlling the addition of organometallic reagents through a metal-chelated intermediate. Therefore, when amide **64** was reacted with excess lithium trimethylsilylacetylide, keto-compound **65** was isolated, not the disubstituted product. Further elaboration of **65** with vinylmagnesium bromide gave tertiary alcohol **66**, which upon desilylation with a catalytic amount of sodium methoxide in methanol, furnished 3-benzyloxymethyl-pent-1-en-4-yn-3-ol (**67**)—the target alkyne.

3. Overview

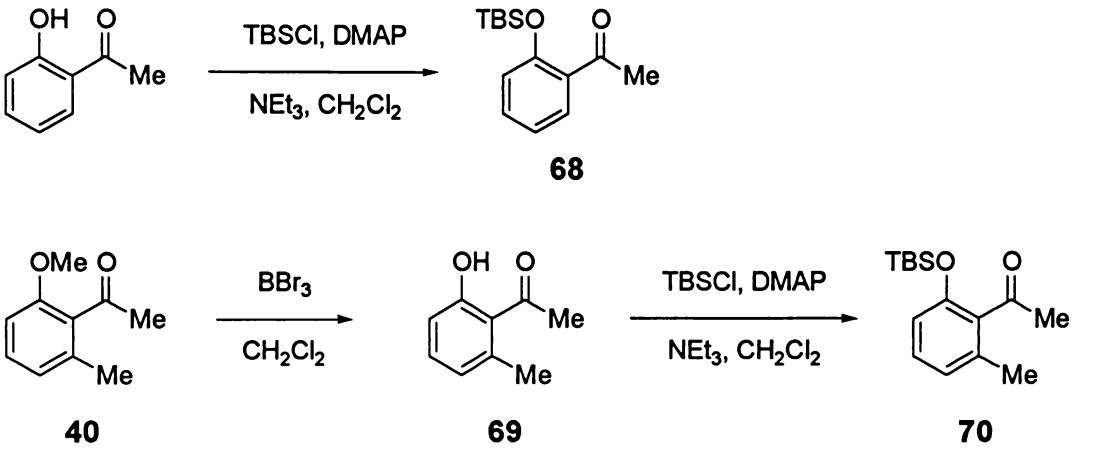
During the experimental trials for finding an appropriate aldehyde and alkynyl side chain synthon, it appears that use of aldehyde **50** and alkyne **67** will give the best chance for coupling. Aldehyde **50** could be coupled in an Aldol condensation reaction and cyclized, then further elaborated into the necessary functionality. Alkyne **67** could be coupled to an appropriate aldehyde with the functionality already installed.

C. Coupling Techniques

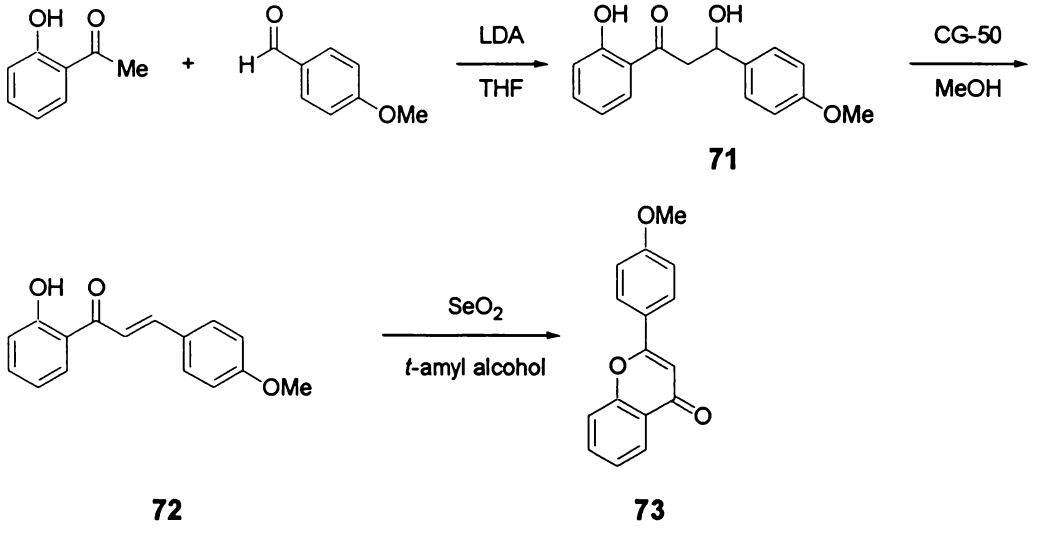
1. Attempts to Generate the Pyranone Ring System through Aldol Condensation Chemistry

To test the plausibility of coupling aldehyde **4** to anthraquinone **3** using aldol chemistry (Scheme 1, path a), a model study was developed. By replacing the anthraquinone ring system with various compounds consisting of a single aromatic ring, it would be possible to create an analog similar in structure to hydramycin. The aromatic analogs would contain the pyranone moiety and a group that could be used to generate the necessary functionality of hydramycin. The aromatic compound would need to have a hydroxyl or protected hydroxyl group at C1 and an acetyl group at C2 to mimic anthraquinone **3** (Scheme 17). By protecting the hydroxyl group of commercially available 2'-hydroxyacetophenone as the *tert*-butyldimethylsilylether, it was possible to generate 2-(*tert*-butyldimethylsilyloxy)acetophenone (**68**). O-Demethylation of **40** with boron tribromide yielded 2-hydroxy-6-methylacetophenone (**69**), which upon silylation gave acetophenone (**70**). These aromatics were used during the the procedures developed during the aldol condensation model study.

Initially, the model study involved the aldol condensation of *p*-anisaldehyde and 2'-hydroxyacetophenone, followed by SeO_2-induced cyclization of the α,β-unsaturated ketone into the pryanone ring system (Scheme 18).[3] Reacting the enolate of 2'-hydroxyacetophenone, generated by LDA, with *p*-anisaldehyde gave β-hydroxy keto-compound **71**. Several methods for the

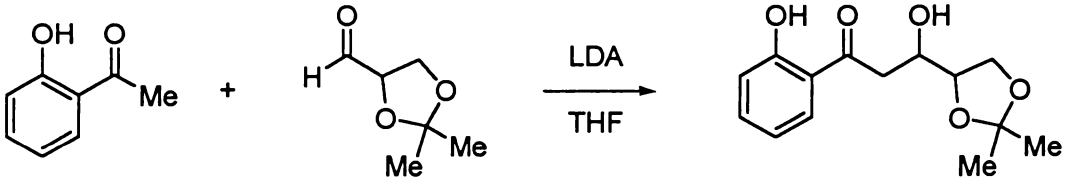


Scheme 17. 2-Acetyl-1-hydroxy- and 2-Acetyl-1-silyloxy- Aromatic Derivatives



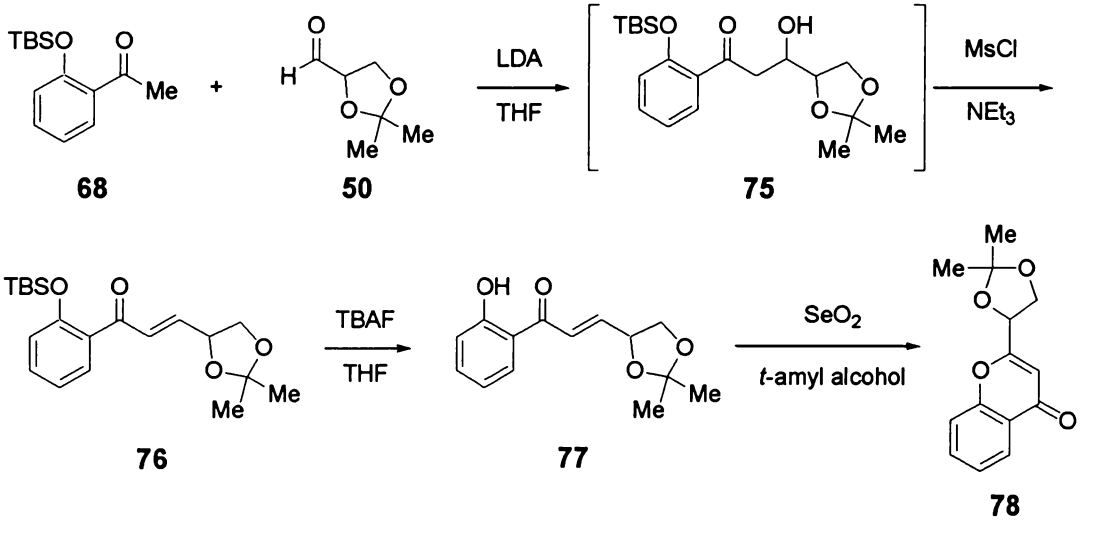
Scheme 18. Synthesis of 2-(4-Methoxyphenyl)-chromen-4-one

dehydration of **71** were explored; however, the use of a weakly acidic cation exchange resin (Amberlite CG-50) in methanol afforded the α,β-unsaturated compound **72** in the best yield. Upon cyclization with SeO_2, the pyranone system was formed generating compound **73**. Since these conditions yielded the desired cyclized product, the model study was expanded to determine if the use of **50** would yield similar results.



50 **74**

From the initial results of the model study, it appeared that reaction of the enolate of 2'-hydroxyacetophenone and **50** could give the needed β-hydroxy keto compound **74**; however, it was found that the use of acetophenoe **68** gave a better yield. Therefore, to generate the new model target—2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-chromen-4-one (**78**)—the aldol condensation of the lithium enolate of **68** and **50** was explored (Scheme 19). There was some concern over the conditions of the dehydration due to the instability of the *O*-isopropylidene group, so it was determined that the intermediate β-hydroxy keto-compound **75** would not be isolated during the procedure, and the dehydration conditions would be altered to the use of MsCl and Et_3N. Desilyation of **76** with TBAF generated phenolic **77**, which upon SeO_2 cyclization gave the model study target as a crude product. However, the yields of both the condensation and cyclization were extremely low, and isolation and purification were difficult. The conditions of the



Scheme 19. Synthesis of 2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-chromen-4-one

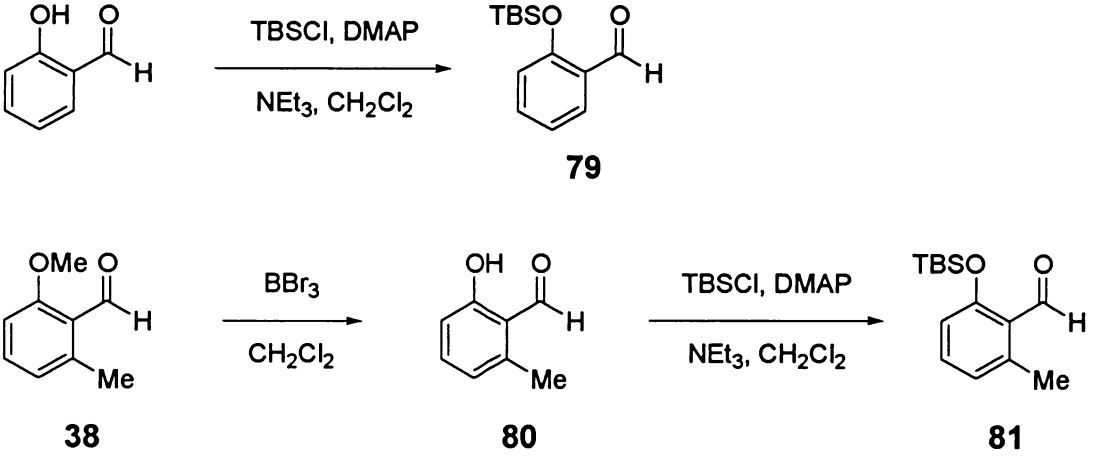
dehydration are varied to try to increase the yield, but to no avail.

Even though the chemistry behind the aldol condensation method for the formation of the pryanone ring system in the model study was successful, the yields in the actual system were too low to allow for further use. Along with the problems of synthesizing an appropriate aldehyde, these low yields led to the discarding of the aldol strategy and developing of the alkynyl coupling strategy (Scheme 1, path b).

2. Alkynyl Coupling and Cyclization for Pyranone Synthesis

A strategy developed for generating the pyranone ring system of hydramycin involved the coupling of an appropriate benzaldehyde to an alkynyl side chain synthon (Scheme 5). Through deprotonation of the alkyne, it was possible to consider a nucleophilic attack of the alkyne on the carbonyl of the derivatized benzaldehyde. The resulting alcohol could be oxidized, leaving an ethynyl ketone that could be cyclized into the needed pyranone via fluoride-induced 6-*endo-digonal* ring closure.[1,6-8] Once the pyranone ring was formed, the necessary functionality could be installed through the alkyne.

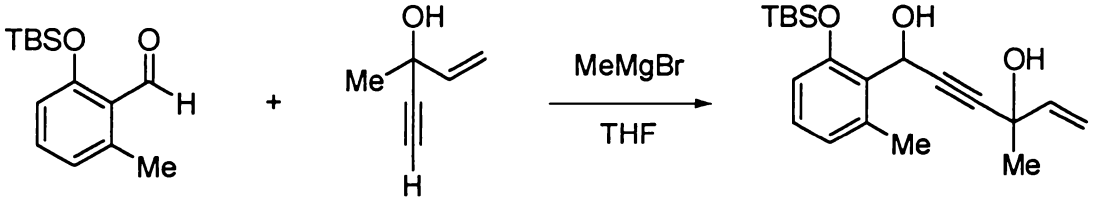
As with the aldol condensation chemistry, a model study was developed that replaced the anthraquinone system (**5**) with a benzaldehyde derivative, which consisted of an ortho silyl ether necessary for the ring closure. Therefore, the synthesis of both 2-(*tert*-butyldimethylsilyloxy)benzaldehyde (**79**) and 2-(*tert*-butyldimethylsilyloxy)-6-methylbenzaldehyde (**81**) were needed (Scheme 20). Protection of salicylaldehyde as the *tert*-butyldimethylsilyl ether (**79**) was



Scheme 20. Synthesis of Derivatized Benzaldehydes

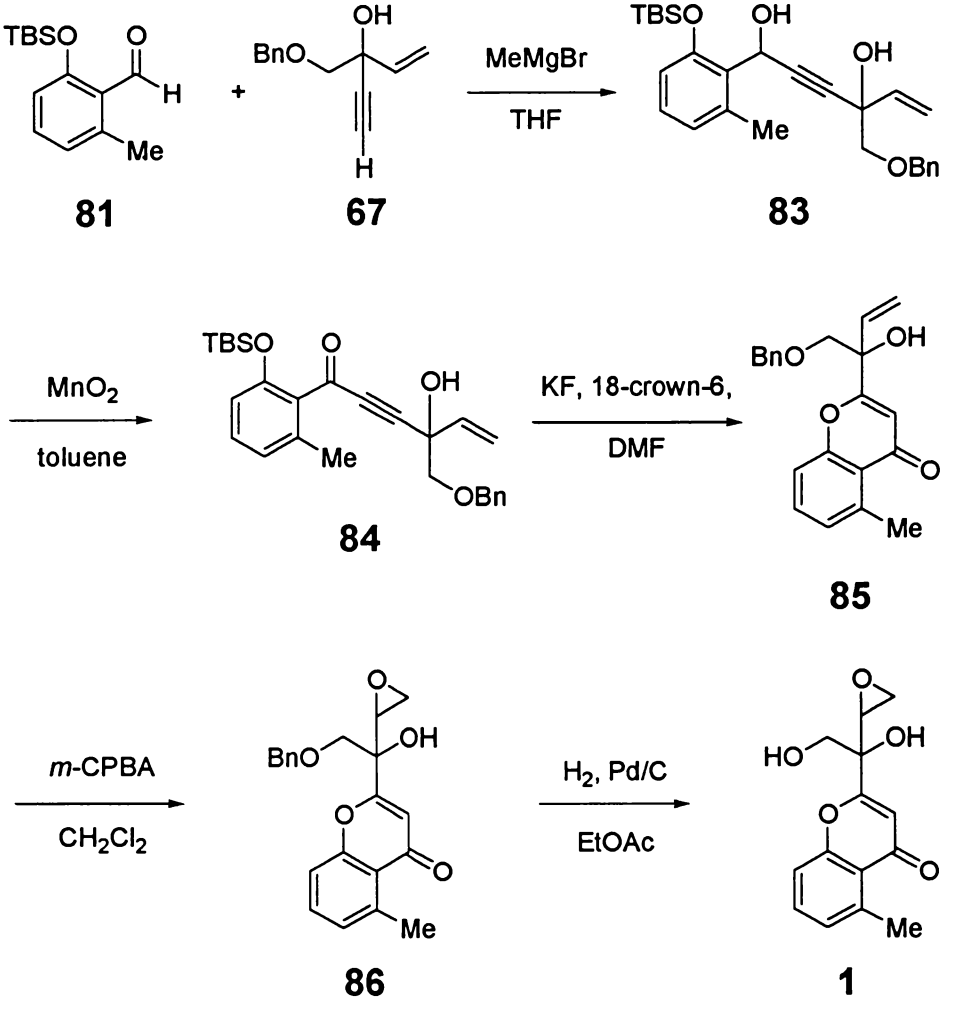
achieved with the use of TBSCl. Compound **80**, from the O-demethylation of **38**, was protected under similar conditions giving benzaldehyde **81**.

To test the procedure for the coupling, the strategy was employed on **81** and commercially available 3-methyl-1-penten-4-yn-3-ol. The dianion generated from the reaction of the alkyne with two equivalents of MeMgBr was reacted with benzaldehyde **81**. The more nucleophilic carbanion reacted with the carbonyl of



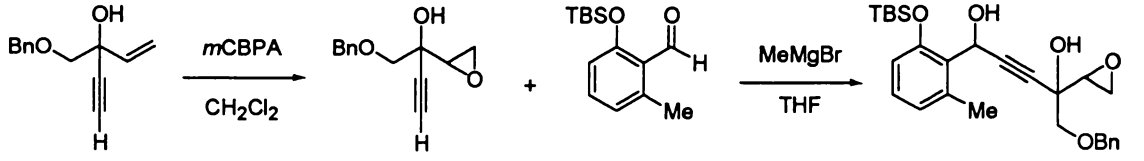
81 **82**

the benzaldehyde generating 1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-4-methylhex-5-en-2-yne-1,4-diol (**82**) in good yield. Since the methodology seemed sound, the strategy was adapted to coupling **81** and the needed alkyne **67**. To generate the dianion, two possibilities were explored: both MeMgBr and *n*-BuLi were each used to remove the hydroxyl and alkynyl protons. It was determined that the grignard reaction gave a higher yield; therefore, when the dianion of **67** was reacted with **81** in route to the desired hydramycin analog **1** (Scheme 21), the diol **83** was obtained. Oxidation of the resulting alcohol was performed with activated MnO_2 giving ethynyl ketone **84**. After fluoride-induced cyclization and epoxidation of the free olefin with *m*-CPBA gave epoxide **86**. O-Debenzylation of **86** was achieved through hydrogenation using palladium-on-carbon in ethyl acetate to avoid saturation of the pyranone ring. The resultant



Scheme 21. Synthesis of 2-(1,2-Dihydroxy-1-oxiranylethyl)-5-methylchromen-4-one

product was the truncated analog **1**. The yield of the epoxidation was low, so it was thought that performing the epoxidation first before coupling might raise the yield. Since the epoxide ring would be susceptible to attack by the MeMgBr, it would be necessary to use *n*-BuLi for deprotonation of the alkyne. The strategy began with with alkyne **87**, which was generated from the epoxidation of **67** with



67 **87** **81** **88**

m-CPBA. The dianion of alkyne **87**, prepared from *n*-BuLi, was coupled to **81** to synthesize diol **88**. Even though the epoxidation yield was higher, the coupling technique with *n*-BuLi gave a poor yield. Hence, the procedure outlined in Scheme 21 was complete and the synthesis of analog **1** was finished.

3. Coupling of Alkyne with *N*-Methoxy-*N*-methyl Derivatives

An alternative method of coupling the aldehyde was generated near the conclusion of Scheme 21. The yield for the oxidation of **83** was moderate, so a strategy that might avoid this step was developed. If the *N*-methoxy-*N*-methyl amide derivative of the aldehyde could be synthesized, the alkyne could be coupled yielding the necessary keto-compound. If successful, this strategy could be employed to anthraquinone acid **45**.

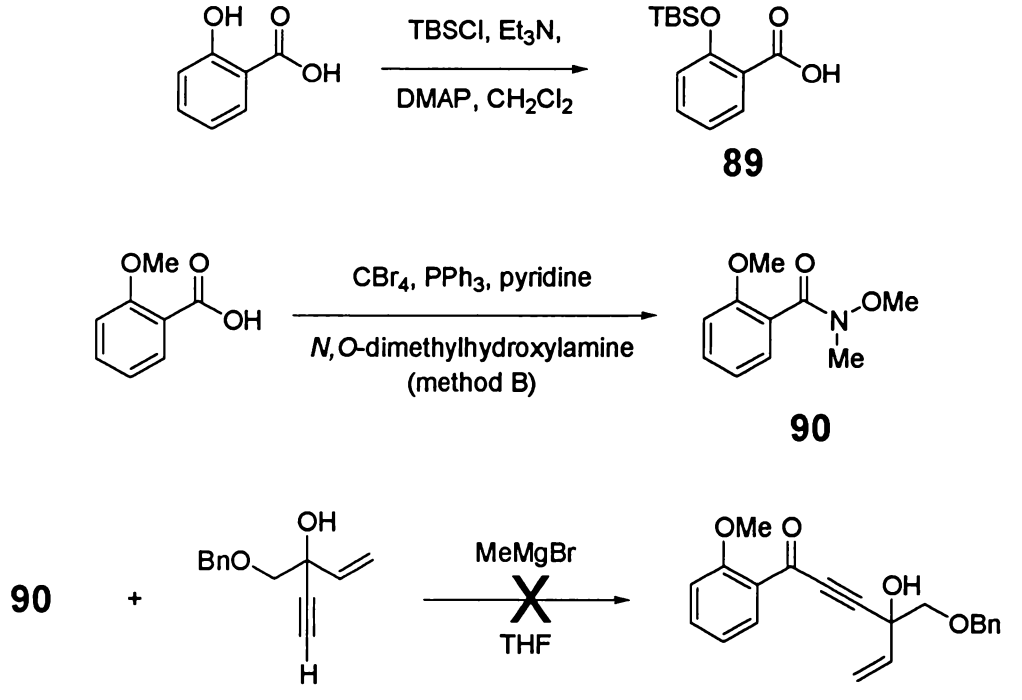
Two unique methods for generating the Weinreb amide was tried: the previously stated method with CDI (method A) and a method utilizing CBr_4, PPh_3,

pyridine and *N,O*-dimethylhydroxylamine hydrochloride (method B).[64] Several benzoic acid derivatives were used to test both methods: salicylic acid, *o*-anisic acid, previously discussed acid **44**, and 2-(*tert*-butyldimethylsilyloxy)benzoic acid (**89**)—synthesized from the silylation of salicylic acid. Reaction of *o*-anisic acid under the conditions of method B gave a poor yield of amide **90**, while no other reactions gave the appropriate amiode product (Scheme 22). Both methods were performed on anthraquinone **45** with no resulting product.

To determine if it was worth pursuing this strategy, amide **90** was reacted with the bromomagnesium salt of alkyne **67**. This reaction gave no coupling product and the amide was not recovered, therefore the idea of generating a *N*-methoxy-*N*-methyl derivatives for coupling was discarded.

4. Overview

The synthesis of analog **1** was important to establish a successful synthetic scheme capable of installation of the proper functionality and the pyranone ring found in **2**. Using the synthesized aldehydo anthraquinone, a synthesis of **2** could be realized. The antibiotic and antitumor activity of analog **1** is predicted to be negligible, since reports have indicated that the minimal structural requirement for efficacy of pyranoanthraquinones is the ABC ring system.[8] However, the synthetic methodology developed during the synthesis of **1** could be expanded to include the full anthraquinone ring moiety yielding **2** and possibly other pluramycinones.



Scheme 22. Reactions during the *N*-Methoxy-*N*-methyl Derivative Study

D. Conclusions and Future Work

The research goal of realizing a viable synthetic strategy for **1** was a success. Through the use of an innovative alkyne synthesis, a fluoride-induced ring closure and creative synthetic strategies, it was possible to generate a compound whose functionality mimics that of hydramcyin. While the failures and complications that arose throughout the research where many, they were instrumental in its development.

The molten salt chemistry generated yielded the aldehydo anthraquinone (1-hydroxy-3-methylanthraquinone-2-carbaldehyde), which gives a platform to expand the methodology of this dissertation into an analog of hydramycin that contains the full anthraquinone ring system and pluramycinone **2** itself. However, there exists other alternative methods for generating the same aldehydo anthraquinone that may prove to be more effective. The potential for producing an anthraquinone derivative from the chemistry of the truncated analog is a real possibility.

IV. EXPERIMENTAL

A. General Experimental Protocol

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were acquired on either a Bruker WP250 (250.13 and 62.89 MHz, respectively) or Varian Mercury 300 (300.09 and 75.46 MHz, respectively) instruments. When $CDCl_3$ was used as the NMR solvent, the reported chemical shifts for the ^{1}H NMR spectra are given in δ units, which represents parts per million (ppm) downfield from the peak from the added standard TMS found at δ 0.0. Reported chemical shifts for ^{13}C NMR spectra are in relation to the solvent triplet found at δ 77.0 in $CDCl_3$. Unless otherwise indicated, the solvent for NMR spectra was $CDCl_3$. Spin–spin splitting patterns are abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, ddt = doublet of doublet of triplets and m = multiplet.

Melting points were determined in open capillary tubes on a Thomas–Hoover Uni-melt melting point apparatus and reported in °C, uncorrected. IR spectra were obtained on a Bomem MB-Series spectrometer as neat liquids or KBr pellets. Elemental analyses were furnished by Atlantic Microlab Inc., Norcross, GA and are within ±0.4% of the theoretical values. Electron-impact mass spectra (EIMS) were obtained on a VG-ZAB-EQ mass spectrometer (Manchester, England) using an ionization potential of 70 eV. Boiling points were determined during distillation and are reported as °C. Column chromatography and TLC were performed with E. Merck Silica Gel 60

products: aluminum–backed plates impregnated with fluorescent indicator F_{254} for TLC, and 40–63 μm mesh silica gel for column chromatography. The solvent used for the development of the plates or elution of the column is indicated for the specific reaction in the experimental section. The detection of the component spots was accomplished with *uv* illumination at 254 nm, spray–heat *p*-anisaldehyde dip, and/or iodine chamber development. The pH of a solution was determined by color comparison on pH Hydrion Paper or via a pH meter.

THF was distilled and collected for immediate use from sodium–benzophenone ketyl. Anhydrous CH_2Cl_2, anhydrous DMSO, anhydrous toluene and anhydrous hexane were dried and distilled from CaH_2, then collected for immediate use. DMF was distilled at reduced pressure from CaH_2, then collected and stored over 4 Å Sieves. Et_3N used as a reagent was dried over CaH_2, distilled, collected and stored over NaOH pellets. Reagent grade acetone was dried and stored over $CaSO_4$. NaH, as a 60% oil dispersion, was washed with several aliquots of hexane, then immediately covered by dry reaction solvent. Anhydrous zinc(II) chloride was generated by extreme heating of hydrated zinc chloride until all moisture was removed. The commercially available 57–86% pure *m*-CPBA was washed with an aqueous pH 7.5 phosphate solution for 20 min, filtered and collected, then dried on a vacuum pump for 24 h. Nitrogen gas, used in a positive-pressure nitrogen line for reactions, was pre-dried via two separate drying tubes before use. All other chemicals used throughout the research were of commercial reagent grade, and unless otherwise noted, were not purified further.

After all extractions, the organic layer was dried with either Na_2SO_4 or $MgSO_4$ and filtered. In general, if the organic solvent was more dense than water, Na_2SO_4 was used; however, if the organic layer was less dense than water $MgSO_4$ was used. After allowing the drying agent and the organic layer to stand for 2–5 min, the mixture was filtered by vacuum filtration to remove the drying agent.

Several ion-exchange resins were used throughout this dissertation. The resin was first swelled in a 1:1 mixture of methanol–water for 1 h, then filtered. The resin was charged by being subjected to either an acidic (1.0 M HCl) or basic (1.0 M NaOH) wash, depending on the resin. After the appropriate wash, the resin was washed thoroughly with water until pH paper indicated the rinse solution was neutral. The resin was finally washed and stored in methanol, so that it could be used in an organic media. Amberlite A-21 is a weakly basic ion-exchange resin, Amberlite IRA-400 is a quaternary ammonium strongly basic resin and Amberlite CG-50 is a weakly acidic carboxylic acid resin.

Several cold-temperature baths were used throughout this research. The temperatures were achieved by the following means: 0 °C bath achieved with ice and water, -10 °C bath achieved with ice, NaCl and water, -15 °C bath achieved with ice and acetone, -50 °C bath achieved with solid carbon dioxide (dry ice) and CH_3CN, and -78 °C bath achieved with dry ice and acetone. All other variable cold baths were achieved by close monitoring of addition of dry ice to acetone by low-temperature thermometer. Heating devices used include both a heating mantle and a silicon oil bath connected through a variable transformer.

B. Friedel–Crafts Coupling in a Molten Salt Mixture of $AlCl_3$ and NaCl.

It is possible to conduct a Friedel–Crafts coupling reaction of an aromatic anhydride and an appropriate aromatic compound using a $AlCl_3$–NaCl molten salt reaction.[30,31,65] The aromatic species can be either a solid or non-solid (oily) reagent; however, different experimental methods are needed for each (discussed below). For both methods, the most important issue is eliminating moisture throughout the entire apparatus. Therefore, all glassware was oven dried and stored in a desiccator filled with $CaSO_4$, and all nitrogen lines were fitted with drying tubes filled with $CaSO_4$. The NaCl was pre-dried in a vacuum oven at 150 °C/0.5 torr. The $AlCl_3$ was weighed under inert atmosphere conditions in a three-neck reaction flask, then quickly flushed with excess nitrogen. Aromatic reagents were placed on vacuum line for 10–12 h to eliminate any moisture.

1. General Procedure for a Coupling of an Anhydride with a Non-solid Aromatic Reagent

The NaCl and $AlCl_3$ were placed in a three-neck flask fitted with a magnetic stirbar, a drying tube, a rubber septum and a solid addition funnel. The anhydride was ground with a mortar and pestle, then placed in the funnel, which was fitted with a gas line providing a continuous flow of dry nitrogen through the system and out the drying tube. The flask was placed in an oil bath and heated to the appropriate temperature; each reaction was found to have a unique reaction temperature, which is specified in the individual experimental section for

the reaction. At approximately 120 °C, the $AlCl_3$–NaCl mixture melted into a gray slurry, which at 140 °C turned into a gray liquid. Once the appropriate temperature was reached, the anhydride was added. After 5 min, the non-solid aromatic reagent was injected via syringe through the septum. During the addition of the non-solid aromatic reagent, the reaction mixture turned a dark maroon-black color, and copious amounts of HCl (g) was generated. The gas was flushed out of the system through the drying tube. For safety reasons, the drying tube can be fitted with a gas line that carries the HCl (g) to a cold-water trap. After all reagents were added, the mixture was allowed to stand for 10–15-min. At this point, the oil bath was removed to cool the reaction. When the mixture began to thicken at 115 °C, ice was added to quench the reaction, followed by the appropriate amount of conc HCl. After the mixture was filtered, and the solid was extracted with 1,2-dichloroethane in a Soxhlet extraction apparatus for 24–48 h.[66] The extraction solution was filtered to remove the boiling chips. The solvent was evaporated, yielding a residue, which was passed through a silica gel column with CH_2Cl_2. The crude solid was crystallized and/or subjected to column chromatography with the appropriate solvent system and analyzed.

2. General Procedure for Coupling of an Anhydride with a Solid Aromatic Reagent

The NaCl and $AlCl_3$ were placed in a three-neck round bottom flask, which was fitted with a magnetic stirbar, a drying tube and two solid addition funnels. The pre-ground anhydride and the solid aromatic reagent were each placed into a solid addition funnel. One of the solid addition funnels was fitted a gas line providing a continuous flow of dry nitrogen through the system and out the drying tube. The flask was placed in an oil bath and heated to the appropriate temperature; each reaction was found to have a unique temperature, which is specified in the individual experimental section. At 120 °C, the $AlCl_3$–NaCl mixture began to melt into a gray slurry and at 140 °C turned into a clear gray liquid. Once the appropriate temperature was reached, the anhydride reagent was added slowly. After 5 min, the second aromatic reagent was added, and the reaction mixture immediately turned a dark maroon color with the release of copious amounts of HCl (g), which was flushed out of the system through the drying tube. For safety reasons, it is possible to replace the drying tube with a gas line which passes through a drying tube into a cold water trap for the escaping HCl (g). Once all reagents were added, the reaction mixture was allowed to stand for 5–20-min (the individual times will be specified in individual sections). The oil bath was removed and the reaction mixture cooled. As the mixture cooled, it began to thicken at 115 °C. At this point, ice was added to the quench the reaction, followed by addition of conc HCl. The mixture was filtered, and the solid was collected and extracted with 1,2-dichloroethane in a Soxhlet

extraction apparatus for 24–48-h.[66] The extraction solution was filtered to remove the boiling chips and evaporated, yielding the crude product. The product was chromtaographed over a silica gel column with CH_2Cl_2. The product was crystallized and/or subjected to column chromatography with the appropriate solvent system and analyzed.

C. Experimental Procedures

1. Anthraquinone Synthon Synthesis

Preparation of 2-Bromo-3-methyl-2-butenal (**30**).

Approximately 100 mL of CH_3CN was placed in a 250-mL round-bottom flask, fitted with a magnetic stir bar, and cooled to -30 °C. The flask was fitted a rubber septum and a nitrogen-filled balloon. To the stirred solution, 10.0 mL (136.2 mmol) of dimethyl sulfide was injected, followed by 6.5 mL (126.2 mmol) of Br_2. After 15 min, a solution of 12.6 mL (130.6 mmol) of 3-methyl-2-butenal dissolved in 10 mL of CH_3CN was added to the bromodimethylsulfonium bromide,[27] which remained *in situ*, forming deep-yellow crystals. When the reaction mixture was warmed to -20 °C, the crystals disappeared, and at -18 °C light-yellow crystals precipitated out, at which time the septum was removed and 100 mL of ethyl ether was added to the solution. The precipitate was collected and washed with additional ether. The solid was dissolved in 250 mL of distilled water containing 13.2 g of $NaHCO_3$. After heating in a 35 °C water bath, the solution was extracted with CH_2Cl_2, dried and concentrated to yield 15.6 g (76%)

of **30**; bp 66 °C/15 torr (lit.[29] 68°C/15 torr). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.38 (s, 3H), 9.74 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.36, 26.07, 122.98, 156.36, 162.71.

Preparation of 2-Bromo-3-methyl-1-trimethylsilyloxy-1,3-butadiene (**31**).

In a 250-mL two-neck round-bottom flask, fitted with a condenser, a rubber septum and a magnetic stir bar, 0.32 g (2.3 mmol) of anhydrous zinc(II) chloride was placed in 50 mL of anhydrous toluene. The flask was placed in an oil bath and fitted with a positive-pressure nitrogen line. To the stirred solution, 13.6 g (83.2 mmol) of 2-bromo-3-methyl-2-butenal was injected. After 10 min., 13.0 mL (102.4 mmol) of TMSCl was injected, followed by a slow injection of 22.0 mL (157.8 mmol) of Et_3N. The reaction was heated to 65 °C for 3 h, then 80 °C for 30 min. To the formed precipitate, 90 mL of distilled hexane was added and the heat was removed. The solution was filtered, concentrated by evaporation and distilled, yielding 10.2 g (52%) of **31**; bp 58 °C/1 torr (lit.[28] 69–71°C/3 torr); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.27 (s, 9H), 1.97 (s, 3H), 4.95 (s, 1H), 5.34 (s, 1H), 6.82 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ -0.36, 20.57, 110.68, 115.18, 137.92, 138.80.

Generation of Jones Oxidation Reagent

A solution of 7.915 g (7.9 mmol) of chromium(VI) oxide dissolved in 14.8 mL of distilled water was placed in a 250-mL round-bottom flask and cooled to 0

°C. As the solution was vigorously stirred, 6.9 mL of concentrated H_2SO_4 was slowly added. The reagent was stored at 0 °C.

Synthesis of 7-bromo-1-hydroxy-6-methylanthraquinone (**35**).

A solution of 0.91 g (5.2 mmol) of 5-hydroxy-1,4-naphthaquinone dissolved in 50 mL of anhydrous toluene was placed in a 100-mL round-bottom flask under nitrogen. Once the flask was cooled to -78 °C, 0.15 mL (1.2 mmol) of boron trifluoride ethyl etherate was added.[26] After 10 min, a solution of 2.06 g (8.8 mmol) of **31** dissolved in 10 mL of anhydrous toluene was added dropwise via syringe. The solution was stirred at -78 °C for 4 h, then allowed to warm to RT over 24 h. The solvent was removed under vacuum, and to the crude organic residue was added 10 mL of acetone and 0.5 mL of Jones oxidation reagent. After stirring for 30 min, the reaction was quenched with 2-propanol and evaporated. The organic residue was subjected to silica gel column chromatography (6:1 hexane–ethyl acetate), yielding 1.32 g (75.7%) of **35**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.32 (d, 1H), 7.69 (dd, 1H), 7.81 (d, 1H), 8.13 (s, 1H), 8.45 (s, 1H), 12.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.63, 119.69, 124.58, 128.87, 129.42, 130.95, 131.49, 132.03, 132.15, 132.27, 133.33, 136.92, 145.89, 162.59, 182.08.

Alternate methods using anhydrous CH_2Cl_2[24], no Lewis acid catalyst and $AlCl_3$ as a Lewis acid catalyst[25] all led to the same product in varying (lower) yields.

Preparation of Ethyl 6-Methyl-2-oxocyclohex-3-enecarboxylate (**16**).

To a solution of 0.8 g (34.8 mmol) of sodium metal dissolved in 350 mL of anhydrous ethanol was slowly added 95.0 mL (0.75 mol) of ethyl acetoacetate. The reaction mixture was cooled to 0 °C, and a solution of 63 mL (0.76 mol) of crotonaldehyde dissolved in 80 mL of anhydrous ethanol was added over 1 h. The mixture was allowed to warm to RT and stir for 24 h, during which time the solution became cloudy and yellow. The mixture was again cooled to 0 °C and saturated with anhydrous HCl (g). A $CaSO_4$ trap was placed between the HCl (g) source and the reaction vessel to ensure that the gas was dry. After saturation, the reaction mixture was allowed to stir at RT for 25 h. Using NMR spectroscopy, it was possible to follow the disappearance of the acetyl peak of the intermediate at δ = 2.2 ppm.[67] If the peak persisted, the reaction mixture was resaturated with dry HCl (g) and allowed to stir for 1 h. Once the monitoring process showed the acetyl peak was gone, the solution was concentrated, and the product was vacuum distilled. At 55 °C/0.5 torr, some decomposition occurred (as seen by a rise in pressure) and persisted for 45 min. After the pressure returned to 0.5 torr, the collection flask was replaced, and 77.9 g (57.0%) of **16** was collected; bp. 92 °C/0.5 torr (lit.[67] 80–95 °C/0.5 torr; lit.[68] 90 °C/0.2 torr).

Preparation of Ethyl 2-Hydroxy-6-methylbenzoate (**17**).

A solution of 77.9 g (0.43 mol) of cyclohexanone **16** dissolved in 150 mL of CCl_4 was placed in a 1-L three-neck round-bottom flask fitted with an addition

funnel and two condensers. The condensers were used to control the copious amounts of HBr (g) generated. A continuous flow of nitrogen was brought in through one condenser and out the other into a water trap. The flask was cooled to 0 °C, and a mixture of 23 mL (0.45 mol) of Br_2 in 110 mL of HOAc was added in a steady stream. After the addition funnel was replaced with a stopper, the reaction was heated to reflux for 18 h. The solution was cooled to RT and diluted with 300 mL of CH_2Cl_2 and 300 mL of water. The organic layer was washed with a saturated solution of $NaHCO_3$ followed by water, then dried, evaporated and steam distilled. The product co-distilled at 102 °C, as white crystals (caution had to be taken, since product would precipitate out in the condenser). After crystallization in methanol–water, the reaction yielded 20.4 g (26.5%) of **17** as white crystals, mp 39–40 °C (lit.[67] 42 °C; lit.[68] 42.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, 3H), 2.55 (s, 3H), 4.43 (q, 2H), 6.71 (d, 1H), 6.84 (d, 1H), 7.27 (dd, 1H), 11.39 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.05, 24.03, 62.17, 115.49, 122.81, 134.01, 137.08, 138.90, 158.91, 167.18.

Preparation of Ethyl 2-Methoxy-6-methylbenzoate (**18**).

A stirred solution of 20.3 g (113 mmol) of phenol **17**, 29.4 g (213 mmol) of anhydrous K_2CO_3 and 14.5 mL (153 mmol) of Me_2SO_4 in 500 mL of anhydrous acetone was refluxed for 7 h. The reaction was monitored by silica gel TLC (CH_2Cl_2). The solution was filtered, evaporated and dissolved in 700 mL of ethyl ether, and Et_3N was added to remove any residual dimethyl sulfate. The organic solution was thoroughly washed with three portions each of the following: water,

0.1 M HCl, and a saturated solution of NaCl. The organic layer was dried, evaporated and distilled, yielding 15.8 g (72.0%) of **18**, bp 89–90 °C/0.8 torr (lit.[67] 89–91 °C/1 torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3H), 2.30 (s, 3H), 3.81 (s, 3H), 4.39 (q, 2H), 6.75 (d, 1H), 6,80 (d, 1H), 7.23 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.07, 18.89, 55.61, 60.86, 108.27, 115.37, 122.14, 129.97, 133.90, 136.02, 168.14.

Preparation of Ethyl 2-(Bis-phenylsulfanylmethyl)-6-methoxybenzoate (**19**).

A 100-mL round-bottom flask, fitted with a positive-pressure nitrogen line and cooled to -78 °C, was filled with 15 mL of anhydrous THF and charged with 8.0 mL of a 2.0 M solution of LDA. A solution of 1.22 g (6.3 mmol) of toluate **18** dissolved in 15 mL of anhydrous THF was added via syringe. To the reddish-orange anionic solution was rapidly added a solution of 2.68 g (12.3 mmol) of phenyl disulfide in 15 mL of anhydrous THF. Once the reaction warmed to RT, the reaction was quenched with 10 mL of HOAc and 30 mL of water. The organic layer was evaporated to an oil and dissolved in ethyl acetate, then washed with water, a 5% solution of NaOH, and a saturated solution of NaCl. The organic layer was dried, evaporated and subjected to silica gel column chromatography (3:1 hexane–CH_2Cl_2), yielding 0.73 g (28.3%) of **19**, mp 73–75 °C (lit.[69] 75–76 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H), 3.80 (s, 3H), 4.28 (q, 2H), 5.70 (s, 1H), 6.81 (d, 1H), 7.21–7.37 (m, 12H).

Synthesis of 1-Hydroxy-2,3-dimethylanthraquinone (**36**).

Following the method outlined in B2, 4.91 g (84.0 mmol) of dry NaCl and 22.02 g (165.1 mmol) of $AlCl_3$ were placed in the reaction system. A pre-ground sample of both 3.13 g (21.1 mmol) of phthalic anhydride and 2.63 g (21.5 mmol) of 2,3-dimethylphenol were placed in the two addition funnels. The system was heated to 175 °C, and the first solid reagent (anhydride) was slowly added. After 5 min, the second reagent was added. After reacting for an additional 10 min,[30] the system was allowed to cool until the reaction mixture began to thicken at 115 °C. At this point, 50 g of ice and 25 mL of concentrated HCl was added. The solid was filtered and extracted. The extraction solution was evaporated and subjected to silica gel column chromatography (CH_2Cl_2). The crude product was crystallized with CH_2Cl_2–ethyl ether, yielding 2.15 g (40.3%) of **36** as orange crystals; mp 219.5–220.5 °C (lit.[70] 220–221.5 °C; lit.[30] 213–215 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.43 (s, 3H), 7.66–8.31 (m, 5H), 13.04 (s, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 12.04, 21.23, 121.44, 127.04, 127.49, 130.46, 133.20, 133,67, 133.99, 134.19, 134.59, 139.41, 146.83, 161.17, 183.00, 188.69. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79 Found: C, 75.88; H, 4.83.

Synthesis of 2,3-Dimethyl-1-methoxyanthraquinone (**46**).

A solution of 0.303 g (1.2 mmol) of **36** dissolved in 125 mL of acetone was placed in a 250-mL round-bottom flask along with a magnetic sitrbar. After 0.674 g (4.8 mmol) of K_2CO_3 and 0.30 mL (4.8 mmol) of MeI was added, the flask was fitted with a condenser and placed in a heating mantle. The mixture was refluxed

for 10 h while being monitored by TLC (CH_2Cl_2). After the mixture was cooled, the solvent was evaporated, and the residue was extracted with CH_2Cl_2 and sequentially washed with water, a saturated NH_4Cl solution and a saturated NaCl solution. The organic layers were collected, dried, evaporated, and subjected to silica gel column chromatography (CH_2Cl_2), which allowed the isolation of orange needle-shaped crystals. These collected crystals were crystallized from CH_2Cl_2–ethyl ether yielding 0.30 g (93.0%) of **46**; mp 166.5–167.5 °C (lit.[30] 165–167 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.43 (s, 3H), 3.90 (s, 3H), 7.73–8.28 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.62, 21.02, 61.18, 123.49, 124.69, 126.55, 127.12, 132.58, 132.69, 133.30, 134.05, 134.85, 139.57, 145.48, 158.82, 182.46, 183.43. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30 Found: C, 76.54; H, 5.19.

Synthesis of 1,8-Dihydroxy-2,3-dimethylanthraquinone (**37**).

Following the method outlined in B2, 1.28 g (21.9 mmol) of dry NaCl and 7.80 g (58.5 mmol) of $AlCl_3$ were placed in the reaction system. A pre-ground sample of both 1.06 g (6.5 mmol) of 3-hydroxyphthalic anhydride and 0.80 g (6.6 mmol) of 2,3-dimethylphenol were placed in the two addition funnels. The system was heated to 210 °C, and the first solid reagent (anhydride) was added. After 5 min, the second reagent was added. After reacting for an additional 10 min, the system was allowed to cool until the reaction mixture began to thicken at 119 °C. At this point, 45 g of ice and 25 mL of conc HCl was added. The solid was filtered and extracted. The extraction solution was evaporated and run

through a silica gel column (CH_2Cl_2). The crude product was crystallized from CH_2Cl_2–ethyl ether, yielding 0.09 g (5.0%) of **37** as dark-orange crystals. ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.44 (s, 3H), 7.28–7.85 (m, 4H), 12.74 (s, 1H), 13.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.07, 60.41, 113.41, 116.16, 119.11, 120.98, 124.59, 129.83, 133.42, 133.78, 136.49, 146.59, 161.18, 162.62, 171.18, 187.65. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51 Found: C, 71.63; H, 4.60.

Synthesis of 1-Hydroxy-3-methylanthraquinone-2-carboxylic Acid (**45**).

Following the method outlined in B2, 6.49 g (111.1 mmol) of dry NaCl and 40.10 g (300.7 mmol) of $AlCl_3$ were placed in the reaction system. One solid addition funnel was charged with 1.94 g (13.1 mmol) of phthalic anhydride, and another solid addition funnel was filled with 2.04 g (12.3 mmol) of **44**. The system was heated to 175 °C, and the phthalic anhydride was slowly added. After 10 min, acid **44** was added and the reaction was allowed to proceed for 15 min. The mixture was cooled until it began to thicken at 115 °C. At this point, 50 g of ice and 25 mL of conc HCl were added. The solid was filtered and extracted. The resulting crude organic material was placed in hot CH_2Cl_2. The insoluble material was collected and crystallized from ethyl acetate–petroleum ether yielding 0.40 g (11.4%) of **45** as bright-yellow crystals, mp 277–278 °C (lit.[71] 276 °C). ^1H NMR (300 MHz, DMSO-d_6) δ 2.29 (s, 3H), 6.75 (d, 1H), 6.99 (d, 1H), 7.47 (dd, 1H), 7.65–7.78 (m, 2H), 8.02 (dd, 1H), 12.18 (br s, 1H), 13.34 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.81, 114.34, 120.41, 126.65, 127.01,

132.66, 132.87, 132.99, 133.08, 134.80, 135.24, 144.10, 158.03, 167.15, 181.68, 187.78. Anal. Calcd for $C_{16}H_{10}O_5$: C, 68.09; H, 3.57. Found: C, 67.28; H, 3.55.

Synthesis of 1-Hydroxy-3-methylanthraquinone-2-carbaldehyde

A solution of 0.18 g (0.6 mmol) of **45** in 100 mL of anhydrous THF was placed in a 250-mL round-bottom flask and cooled to -78 °C. To this solution was injected 1.5 mL (1.5 mmol) of a 1.0 M solution of LAH in ethyl ether. After the reaction was allowed to stir for 1 h, the flask was warmed to RT and allowed to stir for an additional 6 h. The reaction was quenched with sodium sulfate decahydrate and diluted with ethyl ether. After filtration, the filtrate was washed with water and a saturated solution of NaCl. The organic layer was dried, and the solvent was evaporated. The crude organic residue was dissolved in 40 mL of anhydrous CH_2Cl_2 and placed in a 100-mL round-bottom flask. After 1.21 g (5.6 mmol) of PCC was added to the solution, the mixture was refluxed for 10 h. The reaction was quenched with a saturated solution of $NaHCO_3$ and diluted with additional CH_2Cl_2. The organic layer was washed with water and a saturated solution of NaCl, then dried and concentrated. The crude organic residue was subjected to silica gel column chromatography (CH_2Cl_2), yielding 14 mg (8.3%) of 1-hydroxy-3-methylanthraquinone-2-carbaldehyde. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H), 7.49–7.96 (m, 5H), 9.77 (s, 1H), 10.55 (s, 1H). ESI–MS (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{10}O_4$, 267.1; found 267.0; $[M + Na]^+$ calcd for $C_{16}H_{10}O_4$, 289.0; found 288.7.

2. Synthesis of Aldehyde Side Chain Synthon

Synthesis of 2,5-Dihydro-thiophene-3-carbaldehyde (**48**) with Dehydration by MsCl and DIPEA.

In a 1-L round-bottom flask, 14.04 g (92.2 mmol) of 1,4-dithiane-2,5-diol was dissolved in 450 mL of anhydrous CH_2Cl_2. A stirbar was added and the flask was cooled to 0 °C. With stirring, 20 mL (299.3 mmol) of 99% acrolein was added. The flask was fitted with a pressure-equalizing funnel filled with 34.0 mL (243.9 mmol) of Et_3N dissolved in 15 mL of anhydrous CH_2Cl_2, and a positive-pressure nitrogen line. The Et_3N was added over 20 min with continuous stirring, and the mixture was allowed to stand at RT for 12 h. The additional funnel was replaced with a condenser, and the reaction was refluxed for 2 h. The reaction mixture was extracted with 1.0 M HCl, water and a saturated NaCl solution. The crude product **47** was dissolved in 350 mL of anhydrous CH_2Cl_2 and placed in a two-neck round-bottom flask. The flask was fitted with a magnetic stirbar, a condenser and a rubber septum. The flask was cooled to 0 °C and fitted with a positive-pressure nitrogen line. Next, 55.0 mL (315.7 mmol) of DIPEA was injected via syringe into the solution, and the mixture was allowed to sit for 10 min, then 12 mL (155.0 mmol) of MsCl was slowly added via syringe. The reaction was allowed to warm to RT and stir for 4.5 h. The mixture was cooled and extracted with water, 1.0 M HCl and a saturated NaCl solution. The organic layer was dried and evaporated, producing a crude brown oil that was purified by silica gel column chromatography ($CHCl_3$), yielding 3.22 (30.6%) of **48** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.78–3.82 (m, 2H) 3.92–3.96 (m, 2H),

6.89 (t, 1H), 9.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.4, 39.0, 145.6, 148.5, 187.3.

Synthesis of 2,5-Dihydro-thiophene-3-carbaldehyde (**48**) with Dehydration by Molecular Sieves.

In a 1-L round-bottom flask, 11.13 g (73.1 mmol) of 1,4-dithiane-2,5-diol was dissolved in 400 mL of anhydrous CH_2Cl_2. A stirbar was added and the flask was cooled to 0 °C. With stirring, 17.5 mL (235.7 mmol) of 90% acrolein was added. The flask was fitted with a pressure-equalizing funnel, filled with 30.0 mL (215.2 mmol) of Et_3N dissolved in 15 mL of anhydrous CH_2Cl_2, and fitted with a positive-pressure nitrogen line. The Et_3N was added over 20 min with continuous stirring and allowed to stand at RT for 12 h. The additional funnel was replaced with a condenser, and the mixture was refluxed for 2 h. At this point, a catalytic amount of TFA was added, along with 4 Å sieves, and the mixture was refluxed for an additional 4 h. The reaction mixture was cooled and filtered to remove the sieves. The filtrate was extracted with 1.0 M HCl, water and a saturated NaCl solution. The organic layers were combined, dried and evaporated, yielding a viscous brown oil that was subjected to silica gel column chromatography ($CHCl_3$), yielding 5.12 g (61.3%) of **48** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.79–3.82 (m, 2H) 3.93–3.97 (m, 2H), 6.88 (t, 1H), 9.76 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.1, 38.9, 145.6, 148.4, 187.2.

Preparation of 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**51**).

To a stirred solution of 33.50 g (0.249 mol) of anhydrous zinc(II) chloride in 250 mL of dry acetone was added 21.54 g (0.118 mol) of D-mannitol, dried in a vacuum oven at 50 °C for 20 h. The reaction mixture was allowed to stir for 3 h at RT. Unreacted D-mannitol (6.78 g) was removed by vacuum filtration. The filtrate was added to a biphasic solution of 43.2 g of K_2CO_3 dissolved in 44 mL of water and 200 mL of ethyl ether and stirred vigorously for 45 min at RT. The mixture was filtered. The precipitate was washed twice with additional ethyl ether and combined with the filtrate and extracted with 100 mL of a saturated NaCl solution. The organic layer was collected, dried and concentrated, leaving a organic slurry, which was filtered. TLC (2:1 ethyl acetate–petroleum ether) indicated a slight amount of tri-acetonide product. The product was purified by refluxing the collected product in a mixed solution of 1 mL/g of $CHCl_3$ and 10mL/g of petroleum ether for 30 min followed by filtration through fluted filter paper.[49] An additional 100 mL of petroleum ether was added to the filtrate and cooled at 0 °C for 2 h. The solid was collected and dried, yielding 11.77 g (55.4%, based upon amount of D-mannitol originally dissolved) of **51**; mp 118–119 °C (lit.[72] 118–119 °C).

Preparation of Isopropylidene Glyceraldehyde (**50**).

To a stirred suspension of 5.02 g (19.1 mmol) of **51** in 100 mL of a 5% $NaHCO_3$ solution at 0 °C was added dropwise 4.95 (23.1 mmol) of $NaIO_4$ dissolved in 60 mL of water. After the addition was complete, the reaction

mixture was warmed to RT and stirred for 1 h. TLC analysis (2:1 ethyl acetate–petroleum ether) indicated that the reaction was complete. Note: the product spot appeared lower than that of the starting carbohydrate starting material since the acidic TLC plate hydrates the aldehyde. The aqueous layer was extracted with CH_2Cl_2 three times. The organic layers were combined, dried and evaporated. Once the solvent was removed, the reaction yielded 2.14 g (43.0%) of **50**. The product was re-dissolved in 25.0 mL of dry THF (0.659 M solution) and stored over $CaSO_4$ to avoid hydrate formation. IR (KBr) 1736.97.

Preparation of 4-(2-Methoxy-ethoxymethoxymethyl)-2,2-dimethyl-[1,3]dioxolane (**52**).

In a 250 round-bottom flask, fitted with a magnetic stirbar, rubber septum and positive-pressure nitrogen line was placed 1.61 g (40.3 mmol) of cleaned NaH and 150 mL of anhydrous THF. The flask was cooled to 0 °C, and a solution of 3.58 g (27.1 mmol) of solketal dissolved in 5 mL of anhydrous THF was injected via syringe over 15 min. After an additional 15 min at 0 °C, a solution of 5.01 g (40.2 mmol) of MEMCl dissolved in 10 mL of anhydrous THF was injected. The mixture was allowed to warm to RT over 2.5 h, then it was slowly quenched with water and diluted with ethyl ether. The organic layer was washed with a saturated solution of NaCl, dried and evaporated, yielding 4.25 g (71.3%) of **52** as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.43 (s, 3H), 3.39 (s, 3H), 3.54–3.75 (m, 7H), 4.07 (m, 1H), 4.31 (m, 1H), 4.75 (s, 2H). ^{13}C

NMR (63 MHz, $CDCl_3$) δ 25.36, 26.57, 58.80, 66.66, 66.92, 68.75, 71.88, 74.67, 95.56, 109.33.

Preparation of 3-(2-Methoxyethoxymethoxy)-propane-1,2-diol (**53**).

In a 50-mL round-bottom flask, fitted with a magnetic stirbar, rubber septum and positive-pressure nitrogen line, was placed 1.50 g (6.8 mmol) of **52** in 30 mL of anhydrous methanol. To this solution was added via syringe approximately 3 mL of a 0.1 M solution of HCl. After the reaction mixture was allowed to stir for 12 h, $CHCl_3$ was added and separated. The organic layer was washed with water, and a saturated solution of NaCl, dried, and evaporated, yielding 0.34 g (28.0%) of **53**. ^1H NMR (250 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.55–3.74 (m, 9H), 4.77 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 59.00, 63.69, 67.21, 70.34, 70.72, 71.76, 96.02.

Synthesis of 1-(*tert*-Butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-propan-2-ol (**54**).

A solution of 0.53 g (3.0 mmol) of diol **53** in 50 mL of anhydrous CH_2Cl_2 was placed in a 250-mL round-bottom flask. To the flask was added a solution of 0.48 g (3.2 mmol) of TBSCl and 0.02 g (0.1 mmol) of DMAP in 10 mL of anhydrous CH_2Cl_2.[73] The flask was fitted with a rubber septum and a positive-pressure nitrogen line and cooled to -15 °C. Next, 0.5 mL (3.6 mmol) of Et_3N was slowly added via syringe over 15 min. Once the mixture had stirred at RT for 14 h, it was quenched with a saturated solution of NH_4Cl. The organic layer

was washed with water and a saturated solution of NaCl, dried and evaporated. The crude organic residue was subjected to silica gel column chromatography (3:1 petroleum ether–ethyl acetate), yielding 0.53 g (60.0%) of **54** as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 3.40 (s, 3H), 3.55–3.74 (m, 9H), 4.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.44, 25.84, 59.00, 63.92, 66.76, 66.95, 69.54, 70.76, 71.71, 95.97.

Synthesis of 1-(*tert*-Butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-propan-2-one (**55**).

In a 100-mL round-bottom flask fitted with a rubber septum and a positive-pressure nitrogen line was placed 0.25 mL (2.9 mmol) of oxalyl chloride and 30 mL of anhydrous CH_2Cl_2. After the flask was cooled to -78 °C, a solution of 0.4 mL (5.6 mmol) of DMSO dissolved in 5 mL of anhydrous CH_2Cl_2 was injected via syringe over 5 min.[74,75] Stirring was continued at -78 °C for 15 min, at which 0.74 g (2.5 mmol) of **54** dissolved in 10 mL of anhydrous CH_2Cl_2 was injected over 5 min. The mixture was stirred for an additional 45 min at -78 °C. Next, 1.9 mL of Et_3N was injected, and the mixture stirred for 1 h at -78 °C then warmed to RT over 45 min. The reaction was quenched with a saturated solution of NH_4Cl, and the organic layer was separated. The organic layer was washed with water and a saturated solution of NaCl, dried, concentrated and subjected to silica gel column chromatography (5:1 petroleum ether–ethyl acetate), yielding 0.32 g (44.7%) of **55** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.85 (s, 9H), 3.31 (s, 3H), 3.47–3.67 (m, 8H), 4.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -

3.59, 25.63, 29.69, 63.92, 66.95, 69.55, 70.77, 71.71, 95.98, 181.09. IR: 1740.69 cm^{-1}.

Synthesis of 2-*tert*-Butyldimethylsilyloxy-1-(2-methoxyethoxymethoxy)-but-3-en-2-ol (**56**).

In a 50-mL round-bottom flask, 0.37 g (1.3 mmol) of **55** was dissolved in 15 mL of dry THF. The flask, which was fitted with a magnetic stirbar, a rubber septum and a positive-pressure nitrogen line, was cooled to -78 °C. Next, 2.0 mL (2.0 mmol) of a 71.0 M solution of vinylmagnesium bromide in hexane was slowly injected via syringe over 3 min. The mixture was allowed to stand at -78 °C for 1 h, then 4 h at RT. The mixture was quenched with 1 M HCl and extracted with ethyl ether. The organic layer was washed with water and a saturated solution of NaCl, dried, and the solvent was evaporated. The reaction yielded 0.39 g (97.5%) of **56** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 3.39 (s, 3H), 3.54–3.72 (m, 6H), 4.74 (s, 2H), 5.24 (d, *J* = 10.3 Hz, 1H), 5.45 (d, *J* = 17.2 Hz, 1H), 5.92 (dd, *J* = 17.2, 10.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.54, 18.21, 25.78, 58.96, 66.47, 66.90, 71.45, 71.64, 74.51, 95.97, 115.17, 138.59.

Synthesis of 3,4-Bis-(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxymethyl)-but-1-ene (**57**).

To a 100-mL round-bottom flask was added 1.07 g (3.3 mmol) of **56**, 0.80 g (5.3 mmol) of TBSCl and 50 mL of anhydrous CH_2Cl_2. Once the flask was

fitted with a rubber septum, a positive-pressure nitrogen line and cooled to 0 °C, 0.6 mL (5.2 mmol) of 2,6-lutidine was injected via syringe. After the reaction was allowed to warm to RT over 14 h, the mixture was quenched with a saturated solution of NH_4Cl. The organic layer was washed with water and a saturated solution of NaCl, then dried, evaporated and subjected to silica gel column chromatography (3:1 petroleum ether–ethyl acetate), yielding 0.80 g (55.0%) of **57** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.47 (s, 6H), 0.84 (s, 9H), 0.86 (s, 9H), 3.34 (s, 3H), 3.46–3.67 (m, 6H), 4.69 (s, 2H), 5.17 (d, *J* = 10.5 Hz, 1H), 5.38 (d, *J* = 17.4 Hz, 1H), 5.86 (dd, *J* = 17.4, 10.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.62, -3.71, 17.86, 18.12, 25.54, 25.70, 58.87, 66.38, 66.80, 71.35, 71.56, 74.48, 95.86, 115.11, 138.50.

Preparation of Dimethylboron Bromide.

A 50-mL three-neck round-bottom flask with a magnetic stirbar was fitted with a rubber septum, a short-path distillation apparatus and a ground-glass stopper. The collection flask was a pre-weighed 50-mL three-neck round-bottom flask fitted with two rubber septa. The reaction flask was cooled to -45 °C and flushed thoroughly with nitrogen. [Note: the boron tribromide will partially freeze in the reaction flask at -48 °C, so the reaction was performed at -45 °C.] The reaction flask was charged with 4.8 mL (50.8 mmol) of boron tribromide. After 5 min, 7.0 mL (50.5 mmol) of tetramethyl stannate was injected dropwise via syringe.[55] After the reaction mixture was allowed to stand at -45 °C for 0.5 h, the rubber septum in reaction flask was replaced with a ground-glass stopper and

allowed to stand for an additional 0.5 h at RT. The reaction mixture was distilled (oil bath temperature, 65 °C) and the product was collected at 31–32 °C. By weighing the collection flask and eliminating the weight of the added CH_2Cl_2, it was determined that 4.95 g (81.1%) of dimethylboron bromide was synthesized, which exists as a 1.71 M solution in CH_2Cl_2.

Preparation of 2,2-Dimethyl-4-[(4-methoxyphenyl)methoxymethyl]-1,3-dioxolane (**59**).

A slurry mixture of 8.59 g (76.5 mmol) of potassium *tert*-butoxide and 100 mL of dry THF was placed in a 500 mL round-bottom flask, fitted with a rubber septum and a positive-pressure nitrogen line, and cooled to 0 °C. A solution of 9.30 g (70.4 mmol) of 2,2-dimethyl-1,3-dioxolane-4-methanol in 40 mL of dry THF was slowly injected via syringe. After 0.5 h the solution turned to a yellowish-brown color, and at this point 10.4 mL (76.7 mmol) of 4-methoxybenzyl chloride was injected into the reaction mixture. After 18 h, the solvent was evaporated, leaving a residue that was subsequently treated with 80 mL of water and extracted with three portions of 75 mL of ethyl ether. The collected organic layers were combined, extracted with 75 mL of a saturated solution of NaCl, dried, and the ether was evaporated yielding 17.51 g (98.6%) of **59** as a yellow oil.

Alternatively, a slurry of 1.53 g (60.0 mmol) of 95% sodium hydride and 150 mL of dry DMF was placed in a 250-mL round-bottom flask, which was fitted with a magnetic stirbar, rubber septum and positive-pressure nitrogen line, was

cooled to 0 °C. A solution of 7.80 g (59.0 mmol) of 2,2-dimethyl-1,3-dioxolane-4-methanol and 10 mL of dry DMF was slowly injected via syringe. After 10 min, 4.36 g (11.8 mmol) of tetrabutylammonium iodide was added, followed by 8.0 mL (59.0 mmol) of 4-methoxybenzyl chloride. The reaction mixture was stirred at 0 °C for an additional 15 min, then warmed to RT for 12 h. The solvent was evaporated and the organic residue was dissolved into $CHCl_3$ and extracted with water and a saturated solution of NaCl. The organic layer was dried and evaporated.

For both methods, the crude organic residue was subjected to silica gel column chromatography (4:1 petroleum ether–ethyl acetate). The reaction using NaH yielded 2.34 g (18.9%) of the pure product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.41 (s, 3H), 3.43–4.27 (m, 5H), 3.74 (s, 3H), 4.50 (s, 2H), 6.86 (d, 2H), 7.28 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.64, 26.37, 55.67, 66.58, 71.81, 73.33, 74.49, 109.68, 113.94, 129.71, 129.98, 159.05.

Synthesis of 3-[(4-Methoxyphenyl)methoxy]-1,2-propanediol (**60**).

A solution of 17.51 g (69.4 mmol) of **59** dissolved in 150 mL of methanol was placed into a 250-mL round-bottom flask and fitted with a magnetic stirbar. As the solution slowly stirred, 20 mL of 1.0 M HCl was added dropwise. A rubber septum and positive-pressure nitrogen line was added to flask, and the reaction was allowed to stand for 1 h. The solvent was evaporated, and the resulting residue was treated with 150 mL of water and extracted with three portions of 150 mL of ethyl acetate. The organic layers were combined, extracted with 75

mL of a saturated sodium chloride solution, dried, and evaporated yielding **60** as an oil. The crude product was subjected to silica gel column chromatography (2% methanol in $CHCl_3$), which yielded 7.01 g (47.6%) of the product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (s, 2H), 3.81 (s, 3H), 4.40–4.57 (m, 5H), 6.90 (d, 2H), 7.28 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.57, 55.51, 58.08, 73.34, 74.60, 114.00, 129.62, 130.32, 159.44.

Synthesis of 1-*tert*-Butyldimethylsilyloxy-3-[4-(methoxyphenyl)methoxy]-2-propanol (**61**).

A solution of 5.07 g (23.9 mmol) of diol **60** and 100 mL of anhydrous CH_2Cl_2 were placed into a 250-mL round-bottom flask, fitted with a magnetic stirbar, rubber septum and a positive-pressure nitrogen line, and cooled to -78 °C. After 5 min, a solution of 3.77 g (25.0 mmol) of TBSCl and 0.12 g (0.95 mmol) of DMAP in 20 mL of anhydrous CH_2Cl_2 was slowly injected via syringe into the flask. After the solution was allowed to stand for 10 min, 3.8 mL (27.3 mmol) of anhydrous Et_3N was injected into the reaction flask, then allowed to warm to RT over 16 h. The solution was quenched with saturated NH_4Cl and extracted with a saturated solution of NaCl and water. The aqueous layers were combined and extracted with two 50-mL portions of CH_2Cl_2. The organic layers were combined, dried, and evaporated yielding 5.98 g (76.7%) of **61**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.92 (s, 9H), 3.36 (s, 2H), 3.80 (s, 3H), 4.40–4.57 (m, 5H), 6.88 (d, 2H), 7.28 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.78, 26.02, 55.72, 64.56, 64.91, 70.74, 71.98, 73.67, 113.17, 127.55, 128. 61, 159.01.

3. Reactions Involved in Aldol Consendation Chemistry

Synthesis of 3-Hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-propan-1-one (**71**).

In a 100-mL round-bottom flask fitted with a magnetic stirbar, a positive-pressure nitrogen line and rubber septum was placed 40 mL of anhydrous THF. The flask was cooled to -78 °C, then 17 mL (34 mmol) of a 2.0 M solution of LDA in THF–heptane–ethyl benzene was added via syringe. A solution of 1.01 g (7.42 mmol) of 2'-hydroxyacetophenone dissolved in 15 mL of anhydrous THF was slowly added via syringe. After the reaction mixture was allowed to stand at -78 °C for 45 min, a solution of 1.11 g (8.15 mmol) of *p*-anisaldehyde dissolved in 10 mL of anhydrous THF was added and the mixture was allowed to stand for 10 h, slowly warming to RT. The organic reaction mixture was quenched with a saturated NH_4Cl solution and extracted with a saturated NaCl solution and water. The organic layer was dried, evaporated and subjected to silica gel column chromatography (3:1 petroleum ether–ethyl acetate), yielding 0.31 g (15.3%) of **71**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (br s, 1H), 3.31-3.49 (m, 2H), 3.82 (s, 3H), 5.31 (dd, 1H), 6.86–7.72 (m, 8H), 12.10 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 47.36, 55.58, 69.79, 114.25, 118.90, 119.36, 119.63, 127.27, 130.29, 135.08, 137.12, 159.50, 162.80, 205.77.

Synthesis of 1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-propenone (**72**).

To a 100-mL round-bottom flask, fitted with a positive-pressure nitrogen line and a stirbar, was added 0.309 g (1.1 mmol) of **71** and 40 mL of anhydrous

THF. Approximately 1 g of pre-charged Amberlite CG-50 [H^+] ion-exchange resin in methanol was added, and the reaction was refluxed for 18 h. The mixture was filtered through fluted filter paper to remove the resin beads. The organic filtrate was concentrated and subjected to silica gel column chromatography (3:1 petroleum ether–ethyl acetate), yielding 0.178 g (61.6%) of **72**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.95–8.22 (m, 10H), 12.89 (s, 1H).

Synthesis of 2-(4-Methoxyphenyl)chromen-4-one (**73**).

A solution of 0.178 g (0.70 mmol) of **72** dissolved in 50 mL of *tert*-amyl alcohol was placed in a 100-mL round-bottom flask and fitted with a magnetic stirbar. Selenium dioxide (0.112 g, 1.01 mmol) was added, and a rubber septum with a positive-pressure nitrogen line was fitted onto the flask.[3] The reaction mixture was heated to 65 °C and allowed to stand for 18 h. The reaction mixture was filtered through a Celite pad and concentrated. The residue was subjected to silica gel column chromatography (3:1 petroleum ether–ethyl acetate), yielding 16 mg (9.1%) of **73**. Also isolated from the column was 0.11 g (61.8%) of the starting material. This material was redissolved in *tert*-amyl alcohol and placed in a 100-mL round-bottom flask with 95 mg (0.86 mmol) of selenium dioxide, and the reaction repeated. This reaction yielded 25 mg (22.9%) of **73**, giving an overall yield of 22.7%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.76 (s, 1H), 7.04 (d, 2H), 7.43 (dd, 1H), 7.55 (d, 1H), 7.69 (dd, 1H), 7.90 (d, 2H), 8.23 (d, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 28.69, 54.50, 105.18, 113.44, 116.95, 122.91, 123.01, 124.07, 124.65, 127.00, 132.56, 161.36, 162.39, 177.41.

Synthesis of 3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-hydroxy-1-(2-hydroxyphenyl)propan-1-one (**74**).

In a 250-mL round-bottom flask fitted with a magnetic stirbar, a positive-pressure nitrogen line and rubber septum was placed 100 mL of anhydrous THF. Once the flask was cooled to -78 °C, 20 mL (40 mmol) of a 2.0 M solution of LDA in THF–heptane was added via syringe. A solution of 1.50 g (11.02 mmol) of 2'-hydroxyacetophenone dissolved in 15 mL of anhydrous THF was slowly added via syringe. After the reaction mixture was allowed to stand at -78 °C for 2 h, a solution of 1.34 g (10.26 mmol) of *O*-isopropylidene glyceraldehyde dissolved in 10 mL of anhydrous THF was added, and the mixture was allowed to stand for 10 h, slowly warming to RT. The organic reaction mixture was quenched with a saturated NH_4Cl solution and extracted. The aqueous layer was washed with ethyl ether and combined with the original organic layer and concentrated. The crude organic residue was subjected to silica gel column chromatography (3:1 petroleum ether–ethyl acetate), yielding 0.76 g (27.8%) of **74** as a yellow-orange solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.42 (s, 3H), 1.49 (br s, 1H) 3.15 (m, 2H), 4.03–4.17 (m, 3H), 6.93 (dd, 1H), 6.99 (d, 1H), 7.50 (dd, 1H), 7.78 (dd, 1H), 12.02 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.13, 26.36, 26.74, 41.55, 67.04, 69.17, 109.60, 118.62, 119.16, 119.36, 130.16, 136.96, 162.46, 206.17.

Synthesis of 1-[2-(*tert*-Butyldiemthylsilyloxy)phenyl]-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-propenone (**76**).

To a 100-mL round-bottom flask fitted with a magnetic stirbar, rubber septum and a positive-pressure nitrogen line was added 20 mL of anhydrous THF and 8.0 mL (16.0 mmol) of a 2.0 M LDA solution in THF. After the flask was cooled to -78 °C, a solution of 2.73 g (10.9 mmol) of **68** dissolved in 10 mL of anhydrous THF was slowly injected via syringe, and the mixture was stirred for 40 min. Next, 1.33 g (10.2 mmol) of **50** dissolved in 25 mL of anhydrous THF was slowly injected and stirring was continued for 14 h, as the flask was allowed to warm to RT. The mixture was quenched with a saturated NH_4Cl solution and extracted ethyl ether. The aqueous layer was washed with additional ethyl ether. The ether was combined with the original organic layer, which was dried and evaporated, yielding 3.36 g (8.8 mmol; 86.6%) of the crude β-hydroxy intermediate **75** determined by ^1H NMR spectroscopy and TLC. This crude residue was dissolved in 50 mL of anhydrous CH_2Cl_2 and placed in a 100-mL round-bottom flask fitted with a magnetic stirbar and a positive-pressure nitrogen line. After cooling the flask to 0 °C, 1.5 mL (10.8 mmol) of Et_3N was injected, followed by 0.8 mL (10.3 mmol) of MsCl. Once the additions were complete, the flask was warmed to RT and allowed to stir for 2 h, at which time a small aliquot of Et_3N was added and stirring was continued for 1 h. The mixture was quenched with a saturated NH_4Cl solution and extracted. The aqueous layer was washed with additional CH_2Cl_2. The organic layers were combined, dried and evaporated. The crude organic residue was subjected to silica gel column

chromatography (4:3 petroleum ether–ethyl acetate), which yielded 0.4 g (12.9%) of **76**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.96 (s, 9H), 1.41 (s, 3H), 1.44 (s, 3H), 3.67 (dd, 2H), 4.70 (m, 1H), 6.80 (d, 1H), 6.87 (dd, 1H) 6.93 (d, 1H), 7.01 (dd, 1H), 7.35 (dd, 1H), 7.47 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.21, 18.22, 25.71, 26.52, 68.78, 75.42, 110.04, 120.30, 121.40, 130.13, 130.81, 131.58, 132.55, 142.75, 154.06, 193.35.

4. Procedures for Synthesis of Aromatic Derivatives

Preparation of 2-Methoxy-6-methylbenzaldehyde (**38**).

In a 1-L round-bottom flask was combined 5.04 g (37.0 mmol) of 2,3-dimethylanisole, 9.50 g (38.0 mmol) of copper(II) sulfate pentahydrate and 30.85 g (114.1 mmol) of $K_2S_2O_8$ along with 500 mL of 1:1 CH_3CN–water and a magnetic stirbar.[35,36] The flask was fitted with a condenser and heated to reflux while the contents were rapidly stirred. The reaction mixture was monitored by TLC (4:1 petroleum ether–ethyl acetate), and after 2 h the reaction was complete. After the reaction vessel was cooled to RT, 500 mL of ethyl acetate was added. The copper salts can be either dissolved in additional water or filtered off. The organic layer was collected and dried, and the solvent was evaporated. The residue was then subjected to silica gel column chromatography (4:1 petroleum ether–ethyl acetate), yielding 3.77 g (67.8%) of **38**; mp 40–42 °C (lit.[36] 41–42 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.87 (s, 3H), 6.77–6.83 (m, 2H), 7.36 (dd, 1H), 10.62 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.37, 55.61, 108.92, 123.13, 123.95, 134.36, 141.84, 163.04, 192.16.

Preparation of 1-(2-Methoxy-6-methylphenyl)ethanol (**39**).

In a dry 250-mL round-bottom flask was placed 2.55 g (17.0 mmol) of **38**, dissolved in 150 mL of dry THF, and a magnetic stirbar. A rubber septum allowed for the flask to be evacuated and re-pressurized with dry nitrogen. After cooling the flask to -78 °C, 14.0 mL (22.4 mmol) of a 1.6 M solution of MeLi in ethyl ether was slowly injected into the reaction flask via syringe. The mixture was allowed to stand for 10 h, and it slowly warmed to RT. The reaction mixture was quenched slowly with a saturated NH_4Cl solution, then extracted with a saturated NaCl solution and water. The resulting aqueous layers were extracted with additional ethyl ether. The organic layers were combined, dried and evaporated, yielding 2.56 g (90.1%) of **39** as a yellow oil,[34] which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (d, 3H), 2.31 (s, 3H), 3.87 (s, 3H), 5.06 (m, 1H), 6.76–6.81 (m, 2H), 7.11 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.87, 23.38, 55.58, 67.57, 109.43, 117.29, 123.82, 127.72, 135.79, 146.81.

Preparation of 2-Methoxy-6-methylacetophenone (**40**).

A solution of 2.53 g (15.2 mmol) of **39** dissolved in 150 mL of anhydrous toluene was placed, along with a magnetic stirbar, in a 250-mL round-bottom flask. After adding 2.32 g (26.7 mmol) of MnO_2, the flask was fitted with a condenser and refluxed for 14 h.[76-78] The reaction was monitored by TLC (5:1 petroleum ether–ethyl acetate). The reaction flask was cooled, and the solution was filtered through Celite. The filtrate was filtered a second time through a

simple fluted filter paper funnel to eliminate the small amount of MnO_2 that escaped from the original Celite filter. The second filtrate was evaporated, and the organic residue subjected to silica gel column chromatography (5:1 petroleum ether–ethyl acetate), yielding 2.35 g (94.0%) of **40**, as a yellow oil.[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.48 (s, 3H), 3.80 (s, 3H), 6.73-6.80 (m, 2H), 7.20 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 32.1, 55.4, 108.2, 122.8, 129.7, 131.2, 135.2, 156.1, 205.5.

Preparation of 2-Methoxy-6-methylacetophenone (**40**).

A solution of 2.56 g (15.4 mmol) of **39** dissolved in anhydrous CH_2Cl_2 was placed, along with a magnetic stirbar, in a 250-mL round-bottom flask. The flask was cooled to 0 °C and 9.15 g (24.3 mmol) of PDC was added. The flask was fitted with a drying tube and reacted for 30 min at 0 °C, then 14 h at RT. The reaction was monitored by TLC (5:1 petroleum ether–ethyl acetate). The solution was filtered through Celite to remove the majority of the solid impurities and excess PDC. The filtrate was run through a short silica gel column, using CH_2Cl_2 as an elution solvent to remove the remaining PDC from the solution. The second filtrate was evaporated and subjected to silica gel column chromatography (5:1 petroleum ether–ethyl acetate), yielding 1.85 g (73.1%) of **40** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.48 (s, 3H), 3.80 (s, 3H), 6.73–6.80 (m, 2H), 7.20 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 32.1, 55.4, 108.2, 122.8, 129.7, 131.2, 135.2, 156.1, 205.5.

Preparation of 2-Hydroxy-6-methylacetophenone (**69**).

In a three-neck 100-mL round-bottom flask, fitted with an pressure-equalizing funnel, two septa and a positive-pressure nitrogen line, 15 mL of anhydrous CH_2Cl_2 was cooled to -78 °C. The funnel was filled with a solution of 1.16 g (7.06 mmol) of **40** dissolved in 20 mL of anhydrous CH_2Cl_2 and 0.7 mL (7.40 mmol) of boron tribromide was injected via syringe to the flask, and the solution of **40** was added dropwise over 30 min.[76] The mixture was allowed to warm to RT while it stirred for 14 h. The solution was quenched with 50 mL of water. The organic layer was separated, and the aqueous layer was washed with additional CH_2Cl_2. The organic layers were combined, extracted with saturated NaCl, dried and evaporated, leaving a brown oily residue. The oil was passed through a short column of silica gel (1:1 petroleum ether–ethyl ether) to remove polar impurities. The filtrate was distilled using a short-path distillation apparatus, yielding 0.47 g (44.3%) of **69**; bp 82 °C/0.5 torr (lit.[76] 138–142 °C/18 torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H), 2.66 (s, 3H), 6.72 (d, 1H), 6.83 (d, 1H), 7.27 (t, 1H), 12.30 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 33.3, 116.4, 121.6, 123.0, 134.6, 139.4, 162.6, 206.1. In addition to the short-path distillation, it was possible to purify **69** via silica gel column chromatography (7:1 petroleum ether–ethyl acetate). Both purification methods were utilized and were successful.

Synthesis of (2-*tert*-Butyldimethylsilyl)-6-methylacetophenone (**70**).

In a 100-mL round-bottom flask, fitted with a magnetic stirbar, was combined 1.48 g (9.9 mmol) of **69**, 2.19 g (14.5 mmol) of TBSCl, 0.15 g (1.2 mmol) of DMAP and 50 mL of anhydrous DMF. A rubber septum and positive-pressure nitrogen line were added to the flask. After the mixture was allowed to stir for 20 min, 2.5 mL (17.9 mmol) of anhydrous Et_3N was injected via syringe and stirring was continued for 14 h. The reaction mixture was quenched by pouring the mixture over 50 g of ice and 25 mL of a saturated NH_4Cl solution. This mixture was extracted with several aliquots of ethyl ether, which were combined, dried and concentrated yielding 2.26 g (86.7%) of **70** as an orange oil. Further purification was not needed. ^1H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.96 (s, 9H), 2.21 (s, 3H), 2.49 (s, 3H), 6.66 (d, 1H), 6.78 (d, 1H), 7.11 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.31, 18.09, 19.02, 25.62, 32.28, 116.40, 123.20, 129.43, 134.05, 135.31, 151.90, 206.03.

Synthesis of 6-Methylsalicylaldehyde (**80**).

To a stirred solution of 4.30 g (28.6 mmol) of **38** dissolved in 80 mL of anhydrous CH_2Cl_2, under nitrogen at RT, was added dropwise 3.8 mL (40.2 mmol) of boron tribromide. After 1 h, the mixture was carefully poured over 50 g of ice. The aqueous layer was separated and washed with several aliquots of CH_2Cl_2, which were combined with the original organic layer, dried and concentrated into an oil. The crude residue was subjected to flash silica gel column chromatography (CH_2Cl_2) to yield 3.14 g (80.5%) of **80** as an oil. ^1H NMR

(300 MHz, $CDCl_3$) δ 2.60 (s, 3H), 6.70 (d, 1H), 6.80 (d, 1H), 7.37 (dd, 1H), 10.30 (s, 1H), 11.91 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.04, 115.00, 118.42, 137.36, 142.07, 163.06, 195.27.

Synthesis of 2-(*tert*-Butyldimethylsilyloxy)-6-methylbenzaldehyde (**81**).

To a stirred solution of 2.96 g (21.7 mmol) of **80**, 5.20 g (34.5 mmol) of TBSCl, 0.45 g (3.7 mmol) of DMAP in 100 mL anhydrous DMF under nitrogen was added 6.0 mL (43.1 mmol) of Et_3N via syringe at RT. After 14 h, the reaction mixture was poured over 75 g of ice, then extracted with several aliquots of ethyl ether. The organic layers were combined, dried and concentrated, leaving a orange–yellow oil, which was subjected to silica gel column chromatography (2% ethyl acetate in petroleum ether) resulting in 3.30 g (60.6%) of **81** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 6H), 1.00 (s, 9H), 2.56 (s, 3H), 6.72 (d, 1H), 6.80 (d, 1H), 7.29 (dd, 1H), 10.63 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.28, 18.34, 21.55, 25.68, 117.48, 124.58, 125.62, 134.29, 142.09, 160.15, 192.72. Anal. Calcd for $C_{14}H_{22}O_2Si$: C, 67.15; H, 8.86. Found: C, 67.50; H, 8.72.

Synthesis of 2'-*tert*-Butyldimethylsilyloxyacetophenone analog (**68**).

In a 500-mL round-bottom flask, fitted with a magnetic stirbar, was combined 6.98 g (51.3 mmol) of 2'-hydroxyacetophenone, 7.79 g (51.7 mmol) of TBSCl, 0.29 g (2.4 mmol) of DMAP and 250 mL of anhydrous DMF. A rubber septum and positive-pressure nitrogen line were added to the flask. After the mixture was allowed to stir for 20 min, 8.0 mL (57.4 mmol) of anhydrous Et_3N

was injected via syringe, and stirring was continued for 14 h. The reaction mixture was quenched by pouring it over 100 g of ice, and the mixture was extracted with several aliquots of ethyl ether. The organic layer was separated, dried and concentrated leaving an orange oil, which after being subjected to silica gel flash column chromatography (3:1 petroleum ether–ethyl acetate) yielded 12.16 g (94.7%) of **68** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.02 (s, 9H), 2.62 (s, 3H), 6.88 (d, 1H), 6.99 (dd, 1H), 7.35 (dd, 1H), 7.61 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.10, 18.31, 25.74, 31.20, 120.08, 121.05, 129.84, 131.22, 132.76, 154.52, 200.72.

Synthesis of 2-(*tert*-Butyldimethylsilyloxy)benzaldehyde (**79**).

To a stirred solution of 5.86 g (48.0 mmol) of salicylaldehyde, 10.61 g (70.4 mmol) of TBSCl, 0.71 g (5.8 mmol) of DMAP in 150 mL anhydrous DMF under nitrogen was added 10.2 mL (73.2 mmol) of Et_3N via syringe at RT. After 14 h, the reaction mixture was poured over 75 g of ice, then extracted with several aliquots of ethyl ether. The organic layers were combined, dried and concentrated, leaving a orange-yellow oil, which was subjected to silica gel column chromatography (2% ethyl acetate in petroleum ether) resulting in 10.20 g (89.9%) of **79** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 6H), 0.98 (s, 9H), 6.85 (d, 1H), 6.99 (dd, 1H), 7.42 (dd, 1H), 7.76 (d, 1H), 10.43 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.40, 18.26, 25.57, 120.12, 121.36, 127.12, 128.21, 135.62, 158.79, 189.98.

Preparation of (2-Methoxy-6-methylphenyl)methanol (**42**).

To a stirred solution of 2.89 g (19.2 mmol) of **38** dissolved in 100 mL of a 4:1 methanol–CH_2Cl_2 solution at 0 °C was slowly added 3.64 g (96.2 mmol) of $NaBH_4$. After allowing the reaction mixture warm to RT over 14 h, the mixture was quenched with acetone and water, then diluted with CH_2Cl_2. The pH was adjusted to 3.0 by 1.0 M HCl. The organic layer was washed with a saturated solution of NaCl, dried and evaporated, leaving a yellow oil. The oil was subjected to silica gel column chromatography (4:1 petroleum ether–ethyl acetate), yielding 2.53 g of **42** as a yellow-white solid. The product was crystallized from petroleum ether–ethyl acetate, yielding 2.14 g (73.0%) of **42** as white crystals; mp 51.2–52.1 °C (lit.[76] 51–52 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ2.31 (br s, 1H), 2.38 (s, 3H), 3.85 (s, 3H), 4.74 (s, 2H), 6.75 (d, 1H), 6.80 (d,1H), 7.16 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ19.12, 55.42, 57.42, 108.14, 122.97, 127.08, 128.50, 137.77, 158.03.

Synthesis of 2-Methoxymethyl-3-methylanisole (**43**).

In a 100-mL round-bottom flask, 0.61 g (15.3 mmol) of a 60% suspension of NaH in mineral oil was washed with petroleum ether, then immersed in 25 mL of anhydrous THF. The flask was fitted with a rubber septum and positive-pressure nitrogen line, then cooled to -78 °C. To this mixture was added 1.06 g (7.0 mmol) of **42** dissolved in 15 mL of anhydrous THF. The flask was warmed to 0 °C over 1 h, at which time 1.0 mL (10.6 mmol) of Me_2SO_4 was added, and the mixture was allowed to warm to RT and stir for 16 h. The mixture was

quenched with 1.0 M NaOH and extracted with ethyl ether, which was stirred with additional 1.0 M NaOH for 3 h. The organic layer was washed with a saturated solution of NaCl, dried and concentrated, yielding 0.97 g (83.6%) of **43** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.38 (s, 3H), 3.82 (s, 3H), 4.55 (s, 2H), 6.74 (d, 1H), 6.80 (d, 1H), 7.17 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.05, 55.71, 58.09, 65.26, 108.30, 122.74, 124.30, 128.88, 139.87, 158.22.

Synthesis of 3-Methyl-2-vinylanisole (**41**).

To a stirred solution of 8.15 g (22.8 mmol) of methyltriphenylphosphonium bromide in 150 mL of anhydrous THF under nitrogen was added 15.0 mL (24.0 mmol) of a 1.6 M solution of *n*-BuLi in hexane.[37,38] After 20 min, a solution of 3.17 g (21.1 mmol) of aldehyde **38** dissolved in 24 mL of anhydrous THF was injected, and stirring was continued. After an additional 45 min, the reaction was quenched with water and diluted with ethyl ether. The organic layer was washed several times with water and a saturated solution of NaCl, dried and concentrated. Any remaining phosphonium by-products were removed by precipitating out a majority of the phosphonium impurities from ethyl acetate. The filtrate was subjected to silica gel column chromatography (8:1 petroleum ether–ethyl acetate), yielding 2.42 g (77.3%) of **41** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.82 (s, 3H), 5.52 (dd, J = 11.7, 2.4 Hz, 1H), 5.64 (dd, J = 18.0, 2.4 Hz, 1H), 6.73 (d, 1H), 6.78 (d, 1H), 6.79 (d, J = 18.0 Hz, 1H), 7.11 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.80, 55.46, 108.27, 119.33, 122.95, 126.04, 127.50, 131.17, 137.40, 157.58.

Synthesis of 2-Methoxy-6-methylbenzoic Acid (**44**).

To a stirred solution of 6.35 g (42.3 mmol) of **38** in 50 mL of CH_3CN was added 4.8 mL (58.3 mmol) of a 35% wt solution of H_2O_2 in water and 1.4 g (10.1 mmol) of NaH_2PO_4 in 20 mL of water. The reaction flask was cooled to 5 °C and fitted with a pressure-equalizing addition funnel and bubbler line. A solution of 6.68 g (59.1 mmol) of $NaClO_2$ in 70 mL of water was added dropwise from the funnel over 30 min. Release of oxygen gas was monitored by the bubbler. After gas evolution ceased (about 1 h), 0.8 g of Na_2SO_3 was added to destroy any remaining HOCl (generated *in situ*) and H_2O_2. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was separated, washed with a saturated solution of NaCl, dried and concentrated. The crude organic residue was crystallized with ethyl ether–petroleum ether yielding pale-yellow crystals which were further crystallized in water yielding 2.04 g (29.1%) of **44** as white crystals; mp 138.0–138.5 °C (lit.[36] 138–139 °C; lit.[76] 137–139 °C). ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.93 (s, 3H), 6.84 (d, 1H), 6.88 (d, 1H), 7.32 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.80, 56.29, 108.83, 120.81, 123.45, 139.67, 157.19, 170.42.

Synthesis of 2-*tert*-Butyldimethylsilyloxybenzoic Acid (**89**).

A 100-mL round-bottom flask was fitted with a rubber septum and positive-pressure nitrogen line and charged with a solution of 0.53 g (3.8 mmol) of salicylic acid in 50 mL of anhydrous CH_2Cl_2. To the flask was added a solution of 0.59 g (3.9 mmol) of TBSCl and 0.06 g (0.5 mmol) of DMAP in 10 mL of

anhydrous THF. After 10 min, 0.6 mL (4.3 mmol) of Et_3N was injected via syringe and stirring was continued for 5 h. The reaction was quenched with a saturated solution of NH_4Cl. The organic layer was rinsed with additional NH_4Cl, water and a saturated solution of NaCl, then dried and concentrated. The crude organic oil was subjected to silica gel column chromatography (5:2 petroleum ether–ethyl acetate) then crystallized from ethyl acetate–petroleum ether, yielding 0.12 g (12.4%) of **89**, as white crystals. ^1H NMR (300 MHz, $CDCl_3$) δ -0.07 (s, 6H), 0.81 (s, 9H), 4.28 (br s, 1H), 6.88–6.95 (m, 2H), 7.49 (dd, 1H), 7.77 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.12, 25.89, 112.98, 117.20, 119.32, 130.38, 135.80, 161.23, 172.07.

5. Synthesis of Alkyne Synthon

Preparation of Benzyloxyacetic acid (**63**).

In a 250-mL round-bottom flask, fitted with a rubber septum and positive-pressure nitrogen line, was added 64.86 g (0.60 mol) of benzyl alcohol and 3.79 g (164.8 mmol) of sodium metal, and the mixture was heated to 95 °C to fully dissolve the metal. Once the sodium was fully dissolved, 20.11 g (172.6 mmol) of sodium chloroacetate was added. The flask was fitted with a condenser and warmed to 165 °C for 38 h. Concurrently, a second reaction was run using the same procedure with 68.49 g (0.6 mol) of benzyl alcohol, 3.94 g (171.3 mmol) of sodium metal and 20.37 g (174.9 mmol) of sodium chloroacetate. Once cooled to RT, the reaction mixtures were combined, and the excess benzyl alcohol was distilled (55 °C/0.15 torr) away from the remaining waxy product. To this product

400 mL of ethyl ether and 400 mL of water were added and the pH was adjusted to 1.92 with 1.0 M HCl. The organic layer was separated and the aqueous layer was washed with several 50-mL portions of ethyl ether. The organic layers were combined, dried and concentrated. Any residual benzyl alcohol was removed via distillation (56 °C/0.2 torr). Distillation of the product yielded 39.73 g (71.1%) of **63** as a clear oil; bp 124 °C/0.15 torr (lit.[79] 114–115 °C/0.08 torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (s, 2H), 4.62 (s, 2H), 7.29–7.36 (m, 5H), 10.44 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.35, 73.22, 127.97, 128.29, 128.43, 136.47, 175.54.

Synthesis of 2-Benzyloxy-*N*-methoxy-*N*-methylacetamide (**64**).

In a 500-mL round-bottom flask was added 13.70 g (82.4 mmol) of **63**, 14.92 g (92.0 mmol) of CDI and 180 mL of anhydrous THF. The mixture was stirred for 1 h, where all CO_2 evolution had ceased.[61,62] Next, 8.29 g (85.0 mmol) of *N,O*-dimethylhydroxyamine hydrochloride was added, and the reaction was stirred for 50 h. After filtration, the filtrate was diluted with 100 mL of ethyl ether and extracted with several portions of a 1.0 M solution of HCl, followed by a saturated solution of NaCl. The organic layer was dried and concentrated, yielding a clear organic liquid. The product was distilled at 115 °C/0.15 torr, and GC/MS was used to determine the purity of the distillate. The product was stirred with pre-charged Amberlite IRA-400 [OH^-] ion-exchange resin in ethanol for 20 min to remove remaining benzyloxyacetic acid. The resin was filtered off, and the ethanol was evaporated, yielding 13.43 g (77.9%) of **64** as a clear oil. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.62 (s, 3H), 4.29 (s, 2H), 4.67 (s, 2H), 7.35–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.37, 67.31, 73.21, 127.82, 128.03, 128.42, 128.51, 137.45, 221.43.

Synthesis of 1-Benzyloxy-4-trimethylsilylbut-3-yn-2-one (**65**).

A 100-mL round-bottom flask, fitted with a rubber septum and positive-pressure nitrogen line, was charged with 0.30 g (3.0 mmol) of trimethylsilylacetylene, 1.8 mL (2.9 mmol) of a 1.6 M solution of *n*-BuLi in hexane and 40 mL of anhydrous THF and cooled to -78 °C.[80] After the reaction mixture was allowed to stand for 30 min, a solution of 0.31 g (1.5 mmol) of **64** dissolved in 5 mL of anhydrous THF was slowly injected via syringe. The reaction flask was warmed to -10 °C over 1 h and allowed to stand at this temperature for another 1 h. The mixture was cooled to -78 °C, quenched with glacial HOAc, then warmed to 0 °C, at which time 20 mL of a saturated NaCl solution was added along with 20 mL of ethyl ether. The organic layer was removed and washed with additional saturated NaCl solution, while the aqueous layer was washed with several portions of ethyl ether. The organic layers were combined, washed with several portions of a saturated $NaHCO_3$ solution, dried and concentrated, yielding 0.35 g (98.0%) of **65** as a dark red oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 9H), 4.23 (s, 2H), 4.64 (s, 2H), 7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -0.88, 73.34, 75.71, 99.71, 101.27, 127.92, 128.02, 128.47, 137.01, 184.66. EIMS (70 eV) *m/z*: M^+ 246.1 (12), 223.1 (47), 201.1 (19), 173.1 (52), 140.0 (96), 125.0 (100).

Synthesis of 3-Benzyloxymethyl-5-trimethylsilanyl-pent-1-en-4-yn-3-ol (**66**).

To a stirred solution of 0.34 g (1.4 mmol) of **65** in 40 mL of anhydrous THF, under nitrogen and at -78 °C, was added via syringe 5.0 mL of a 1.0 M solution of vinylmagnesium bromide in hexane. The reaction mixture was allowed to slowly warm to RT over 18 h, then the reaction was cooled to 0 °C and quenched with a saturated NH_4Cl solution and diluted with ethyl ether. After separation, the aqueous layer was washed with several small portions ethyl ether. The organic layers were combined, washed with a saturated NaCl solution, dried and evaporated, yielding 0.38 g (99.7%) of **66** as a dark oil, which was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H), 2.92 (br s, 1H), 3.49 (d, *J* = 9.3 Hz, 1H), 3.58 (d, *J* = 9.3 Hz, 1H), 4.68 (s, 2H), 5.27 (d, *J* = 10.2 Hz, 1H), 5.63 (d, *J* = 17.1 Hz, 1H), 5.91 (dd, *J* = 17.0, 10.0 Hz, 1H), 7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -0.15, 71.09, 73.55, 76.42, 90.56, 104.54, 116.69, 127.60, 127.75, 128.40, 137.30, 137.76.

Synthesis of 3-Benzyloxymethyl-pent-1-en-4-yn-3-ol (**67**).

In a 100-mL round-bottom, chilled to 0 °C and under nitrogen, was placed 40 mL of anhydrous methanol and 0.38 g (1.4 mmol) of **66**. To this stirred solution was injected via syringe a catalytic amount of a 25 wt % solution of sodium methoxide in methanol.[6] The flask was warmed to RT for 3 h before being quenched with a saturated NH_4Cl solution and extracted with ethyl ether. The aqueous layer was washed with several small portions of ethyl ether. The organic layers were combined, washed with water, washed with a saturated NaCl

solution, dried and evaporated. The crude product was purified by silica gel column chromatography (9:1 petroleum ether–ethyl acetate) yielding 0.24 g (87.4%) of **67** as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 1H), 2.98 (br s, 1H), 3.49 (d, *J* = 9.3 Hz, 1H), 3.59 (d, *J* = 9.3 Hz, 1H), 4.68 (s, 2H), 5.29 (d, *J* = 10.5 Hz, 1H), 5.64 (d, *J* = 16.8 Hz, 1H), 5.91 (dd, *J* = 17.1, 10.5 Hz, 1H), 7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.67, 73.71, 73.86, 76.36, 83.29, 117.02, 127.72, 127.86, 128.45, 136.92, 137.49. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.37; H, 6.98.

Synthesis of 1-Benzyloxy-2-oxiranyl-but-3-yn-2-ol (**87**).

To a solution of 0.56 g (2.8 mmol) of **67** in 75 mL of anhydrous CH_2Cl_2 at 0 °C under nitrogen was added 0.99 g (5.8 mmol) of *m*-CPBA and 1.22 g (8.6 mmol) of Na_2HPO_4. After the reaction mixture was stirred at RT for 17 h, it was diluted with a saturated solution of $Na_2S_2O_3$ and a saturated solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water, a saturated solution of NaCl, dried and concentrated. The crude organic residue was subjected to silica gel column chromatography (6:1 petroleum ether–ethyl acetate), yielding 0.13 g (21.5%) of **87** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 1H), 2.77 (m, 1H), 2.94 (m, *J* = 10.0, 5.1, 2.7 Hz, 1H), 3.10 (d, *J* = 9.3 Hz, 1H), 3.26 (m, 1H), 3.67 (m, 1H), 4.65 (s, 2H), 7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.89, 54.26, 68.64, 73.63, 73.89, 74.39, 81.33, 127.59, 127.75, 128.34, 137.36. ESI–MS (*m/z*): $[M + Na]^+$ calcd for $C_{13}H_{14}O_3$, 241.2; found 241.0; $[M + K]^+$ calcd for $C_{13}H_{14}O_3$, 257.3; found 256.9.

6. Alkynyl Coupling Procedures

Synthesis of 1-(2-*tert*-Butyldimethylsilyloxy-6-methylphenyl)-4-methyl-hex-5-en-2-yne-1,4-diol (**82**).

To a solution of methylmagnesium bromide (1.8 mL, 3 M in ethyl ether, 5.4 mmol) in 10 mL of anhydrous THF was added a solution of 0.241 g (2.51 mmol) of the acetylene in 10 mL of anhydrous THF at 0 °C under nitrogen and the mixture stirred at 50 °C for 3 h. A solution of 0.609 g (2.43 mmol) of **81** dissolved in 5 mL of anhydrous THF was added at RT, and the entire reaction mixture stirred for an additional 2 h. The reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with several portions of ethyl acetate. The organic layers were combined, extracted with a saturated solution of NaCl, separated, dried and concentrated. The crude organic residue was subjected to silica gel column chromatography. The initial solvent system was 6:1 petroleum ether–ethyl acetate to elute remaining aldehyde **81**, then solvent system slowly changed to 1:1 petroleum ether–ethyl acetate to elute product. The reaction yielded 0.54 g (63.8%) of **82** isolated as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 6H), 1.04 (s, 9H), 1.48 (s, 3H), 2.45 (s, 3H), 3.78 (d, 1H), 5.03 (dd, 1H, J = 6.2, 10.2 Hz), 5.39 (dd, 1H, J = 17.4, 10.2 Hz), 5.92 (m, 2H), 6.68 (d, 1H), 6.76 (d, 1H), 7.04 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.03, 18.40, 19.85, 26.05, 29.85, 59.38, 68.21, 84.80, 86.15, 113.48, 116.44, 124.00, 128.30, 128.77, 137.32, 141.65, 153.12. Anal. Calcd for $C_{20}H_{30}O_3Si$: C, 69.32; H, 8.73. Found: C, 69.05; H, 8.93.

Synthesis of 4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-hex-5-en-2-yne-1,4-diol (**83**) via the Bromomagensium Salt of **67**.

In a 100-mL round-bottom flask, a solution of methylmagnesium bromide (4.8 mL, 3 M in ethyl ether, 14.4 mmol) in 5 mL of anhydrous THF was cooled to 0 °C and placed under nitrogen. A solution of 1.45 g (7.2 mmol) of acetylene **67** dissolved in 10 mL of anhydrous THF was added with syringe and the reaction mixture was warmed to 50 °C for 2 h. At this point the reaction was cooled to RT and a solution of 1.60 g (6.4 mmol) of aldehyde **81** dissolved in 5 mL of anhydrous THF was added via syringe. After stirring for 14 h at RT, the reaction mixture was quenched with a saturated solution of NH_4Cl and extracted with several portions of ethyl acetate. The organic layers were combined, extracted with a saturated solution of NaCl, separated, dried and concentrated. The crude organic residue was subjected to silica gel column chromatography (6:1 petroleum ether–ethyl acetate; R_f = 0.06) to elute starting material, then the solvent was changed (3:1 petroleum ether–ethyl acetate; R_f = 0.30) yielding 1.51 g (52.2%) of **83** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 6H), 1.02 (s, 9H), 2.23 (s, 1H), 2.44 (s, 3H), 2.91 (br s, 1H), 3.45 (d, 1H), 3.52 (d, 1H), 4.58 (s, 1H), 5.20 (d, 1H), 5.53 (d, 1H), 5.82–5.93 (m , 2H), 6.66–6.79 (m, 2H), 7.05 (dd, 1H), 7.27–7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.97, 18.25, 19.76, 25.91, 59.14, 70.77, 73.55, 76.41, 83.82, 85.79, 116.50, 124.14, 127.62, 128.36, 128.68, 137.26, 137.35, 137.56, 137.63, 137.67, 153.17. ESI–MS (*m/z*): $[M + Na]^+$ calcd for $C_{27}H_{36}O_4Si$, 475.2; found 475.1; $[M + K]^+$ calcd for $C_{27}H_{36}O_4Si$, 491.2; found 491.0.

Synthesis of 4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-hex-5-en-2-yne-1,4-diol (**83**) via the Lithium Salt of **67**.

In a 50-mL round-bottom flask, a solution of 6.4 mL (1.6 M; 10.2 mmol) of *n*-BuLi in 3 mL of anhydrous THF was cooled to 0 °C and placed under nitrogen. To this solution was added 1.02 g (5.0 mmol) of **67** dissolved in 5 mL of anhydrous THF via syringe and stirring continued at 0 °C for 15 min. Next, a solution of 1.20 g (4.8 mmol) of **81** dissolved in 3 mL of anhydrous THF was added and stirring continued at 0 °C for 30 min and at RT for 4 h. The reaction was quenched with a saturated solution of NH_4Cl and diluted with ethyl acetate. The organic layer was washed with water and a saturated solution of NaCl, then dried and concentrated. The resulting organic residue was subjected to silica gel column chromatography (6:1 petroleum ether–ethyl acetate; R_f = 0.06) to elute starting material then the solvent was changed (3:1 petroleum ether–ethyl acetate; R_f = 0.31), yielding 0.55 g (25.3%) of **83** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 6H), 1.02 (s, 9H), 2.23 (s, 1H), 2.43 (s, 3H), 2.90 (br s, 1H), 3.43 (d, 1H), 3.51 (d, 1H), 4.58 (s, 1H), 5.19 (d, 1H), 5.52 (d, 1H), 5.80–5.92 (m , 2H), 6.65–6.79 (m, 2H), 7.05 (dd, 1H), 7.27–7.33 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -3.98, 18.25, 19.77, 25.92, 59.15, 70.79, 73.56, 76.42, 83.84, 85.81, 116.53, 124.19, 127.63, 128.39, 128.71, 137.28, 137.36, 137.59, 137.65, 137.70, 153.20. ESI–MS (*m/z*): $[M + Na]^+$ calcd for $C_{27}H_{36}O_4Si$, 475.2; found 475.1; $[M + K]^+$ calcd for $C_{27}H_{36}O_4Si$, 491.2; found 491.0.

Synthesis of 5-Benzyloxy-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-4-oxiranyl-pent-2-yne-1,4-diol (**88**).

To a solution of 0.13 g (0.6 mmol) of **87** in 20 mL of anhydrous THF, cooled to -78 °C, was added 0.8 mL (1.3 mmol) of a 1.6 M solution of *n*-BuLi in hexane. After the solution was stirred for 20 min, a solution of 0.19 g (0.8 mmol) of **81** dissolved in 3 mL of anhydrous THF was injected via syringe and stirring continued for 2 h at -78 °C. The reaction was quenched with a saturated solution of NH_4Cl and diluted with ethyl acetate. The organic layer was separated and washed with water and a saturated solution of NaCl, then dried and concentrated. The crude organic residue was subjected to silica gel column chromatography (6:1 petroleum ether–ethyl acetate), yielding 56 mg (20.0%) of **88** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.23 (s, 6H), 0.92 (s, 9H), 1.3 (br s, 1H), 2.27 (s, 3H), 2.71–2.90 (m, 3H), 3.21 (m, 1H), 3.63 (m, 2H), 4.58 (m, 2H), 5.78 (s, 1H), 6.65 (d, 1H), 6.75 (d, 1H), 7.08 (dd, 1H), 7.27–7.34 (m, 5H).

Synthesis of 4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-4-hydroxy-hex-5-en-2-yn-1-one (**84**).

In a 25-mL round-bottom flask, fitted with a condenser and a positive-pressure nitrogen line, was placed 0.32 g (0.70 mmol) of **83** dissolved in 15 mL of anhydrous toluene and 3.12 g (35.9 mmol) of MnO_2. The mixture was refluxed for 5 h then filtered through a Celite pad using ethyl acetate and ethyl ether. After the solvent was evaporated, the resulting yellow residue was subjected to silica gel column chromatography (7:1 petroleum ether–ethyl acetate; R_f = 0.23),

yielding 74 mg (23.5%) of **84** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.95 (s, 9H), 2.29 (s, 3H), 3.12 (br s, 1H), 3.49 (d, 1H), 3,60 (d, 1H), 4.62 (s, 2H), 5.29 (d, J = 10.5 Hz, 1H), 5.60 (d, J = 17.1 Hz, 1H), 5.83 (dd, J = 17.1, 10.4 Hz, 1H), 6.67 (d, 1H), 6.78 (d, 1H), 7.15 (dd, 1H), 7.30 (m, 5H). IR: 1697 cm^{-1}. ESI–MS (*m/z*): $[M + H]^+$ calcd for $C_{27}H_{34}O_4Si$, 451.2; found 451.0; $[M + Na]^+$ calcd for $C_{27}H_{34}O_4Si$, 473.2; found 473.0; $[M + K]^+$ calcd for $C_{27}H_{34}O_4Si$, 489.2; found 489.0.

Synthesis of 2-(1-Benzyloxymethyl-1-hydroxyallyl)-5-methylchromen-4-one (**85**).

In a 25-mL round-bottom flask, fitted with a rubber septum and positive-pressure nitrogen line, was placed 74 mg (160 µmol) of **84**, 96 mg (360 µmol) of 18-crown-6 and 5 mL of anhydrous DMF. To this solution at 0 °C was added 28 mg (480 µmol) of spray-dried KF.[1,7] The reaction was allowed to stirred at RT for 2 h. The reaction mixture was quenched with a saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with a saturated NaCl solution, dried, and concentrated. The crude organic residue was subjected to silica gel column chromatography (3:1 petroleum ether–ethyl acetate; R_f = 0.14), yielding 53 mg (96.3%) of **85** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.63 (d, 1H), 3.75 (d, 1H), 4.61 (dd, 2H), 5.26 (d, J = 10.8 Hz, 1H), 5.49 (d, J = 17.1 Hz, 1H), 6.07 (dd, J = 17.3, 10.7 Hz, 1H), 6.14 (s, 1H), 6.92 (d, 1H), 6.98 (d, 1H), 7.30 (m, 5H), 7.46 (dd, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.78, 73.60, 75.22, 75.45, 109.91, 115.64, 119.25, 124.81, 127.68, 127.76, 127.93, 128.33, 128.38, 136.67, 137.67, 140.25, 147.12, 166.44, 184.98.

ESI–MS (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{20}O_4$, 337.1; found 336.9; $[M + Na]^+$ calcd for $C_{21}H_{20}O_4$, 359.1; found 359.0; $[M + K]^+$ calcd for $C_{21}H_{20}O_4$, 375.1; found 374.9.

Synthesis of 2-(2-Benzyloxy-1-hydroxy-1-oxiranylethyl)-5-methylchromen-4-one (**86**).

To a stirred solution of 0.15 g (0.5 mmol) of **85** and 0.33 g (2.3 µmol) of Na_2HPO_4 in 10 mL of anhydrous CH_2Cl_2 was added 0.47 g (2.8 mmol) of *m*-CPBA at 0 °C. After the reaction mixture was stirred at RT for 10 h, it was quenched with a saturated solution of $Na_2S_2O_3$ and a saturated solution of $NaHCO_3$ then extracted with ethyl acetate. The organic layer was washed with a saturated solution of NaCl, then it was dried and concentrated. The crude organic residue was subjected to silica gel column chromatography (1:1 petroleum ether–ethyl acetate; R_f = 0.11) and the final product crystallized from petroleum ether–ethyl acetate, yielding 12 mg (7.6%) of **86** as pale-yellow crystals. ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 3H), 2.96 (dd, 1H), 3.52 (dd, 1H), 3.77 (d, 1H), 3.91 (d, 1H), 4.12 (dd, 1H), 4.58 (dd, 2H), 6.63 (s, 1H), 7.21–7.48 (m, 6H), 7.59 (d, 1H), 8.00 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.75, 43.55, 53.15, 65.16, 70.58, 73.71, 100.125, 111.08, 111.36, 115.82, 127.65, 127.79, 128.54, 129.59, 132.62, 133.22, 133.60, 139.47, 188.68. ESI–MS (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{20}O_5$, 353.4; found 353.2; $[M + Na]^+$ calcd for $C_{21}H_{20}O_5$, 375.4; found 375.3; $[M + K]^+$ calcd for $C_{21}H_{20}O_5$, 391.5; found 391.3.

Synthesis of 2-(1,2-Dihydroxy-1-oxiranylethyl)-5-methylchromen-4-one (**1**).

In a 25-mL round-bottom flask was placed 12 mg (34 µmol) of **86** dissolved in 7 mL of anhydrous ethyl acetate along with 82 mg of 10% palladium-on-carbon. After the flask was fitted with a magnetic stirbar and a rubber septum, hydrogen gas was introduced to the flask. The reaction was allowed to stir for 20 h, after which the hydrogen gas source was removed and the mixture was passed through a small portion of Celite to remove the carbon. The crude material was purified via a silica gel preparative plate (3:5 petroleum ether–ethyl acetate; R_f = 0.21), yielding 2 mg (22.4%) of **1** as a pale solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (s, 3H), 3.84 (dd, 2H), 4.12 (dd, 1H), 4.22 (dd, 2H), 6.84 (s, 1H), 7.48 (dd, *J* = 7.5, 7.6 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 8.11 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.32, 39.93, 53.74, 71.34, 123.96, 125.23, 125.93, 127.68, 129.05, 129.97, 131.17, 164.24, 169.99, 185.86. ESI–MS (*m/z*): $[M + H]^+$ calcd for $C_{14}H_{14}O_5$, 263.3; found 000.0; $[M + Na]^+$ calcd for $C_{14}H_{14}O_5$, 285.2; found 000.0; $[M + K]^+$ calcd for $C_{14}H_{14}O_5$, 301.3; found 000.0.

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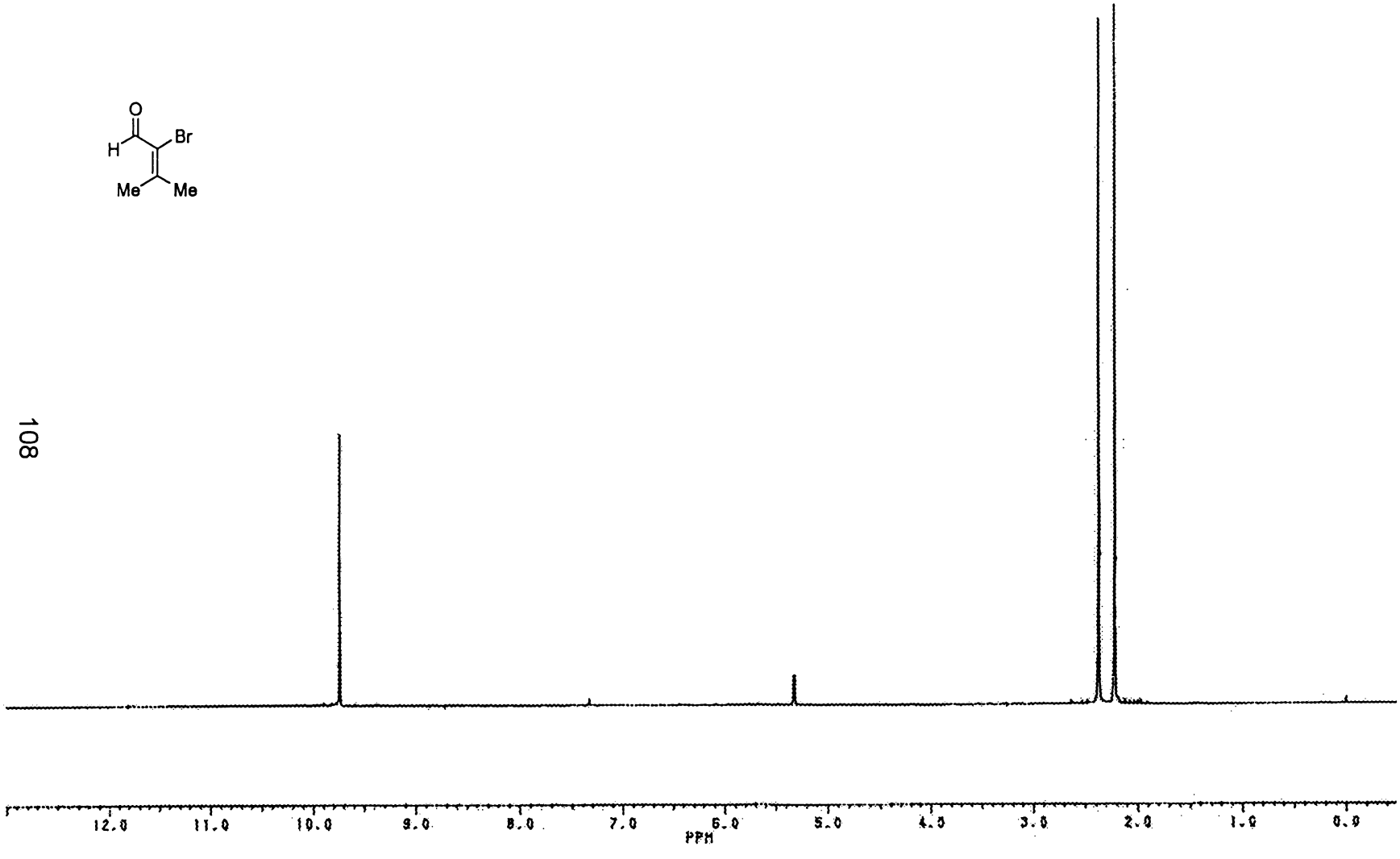
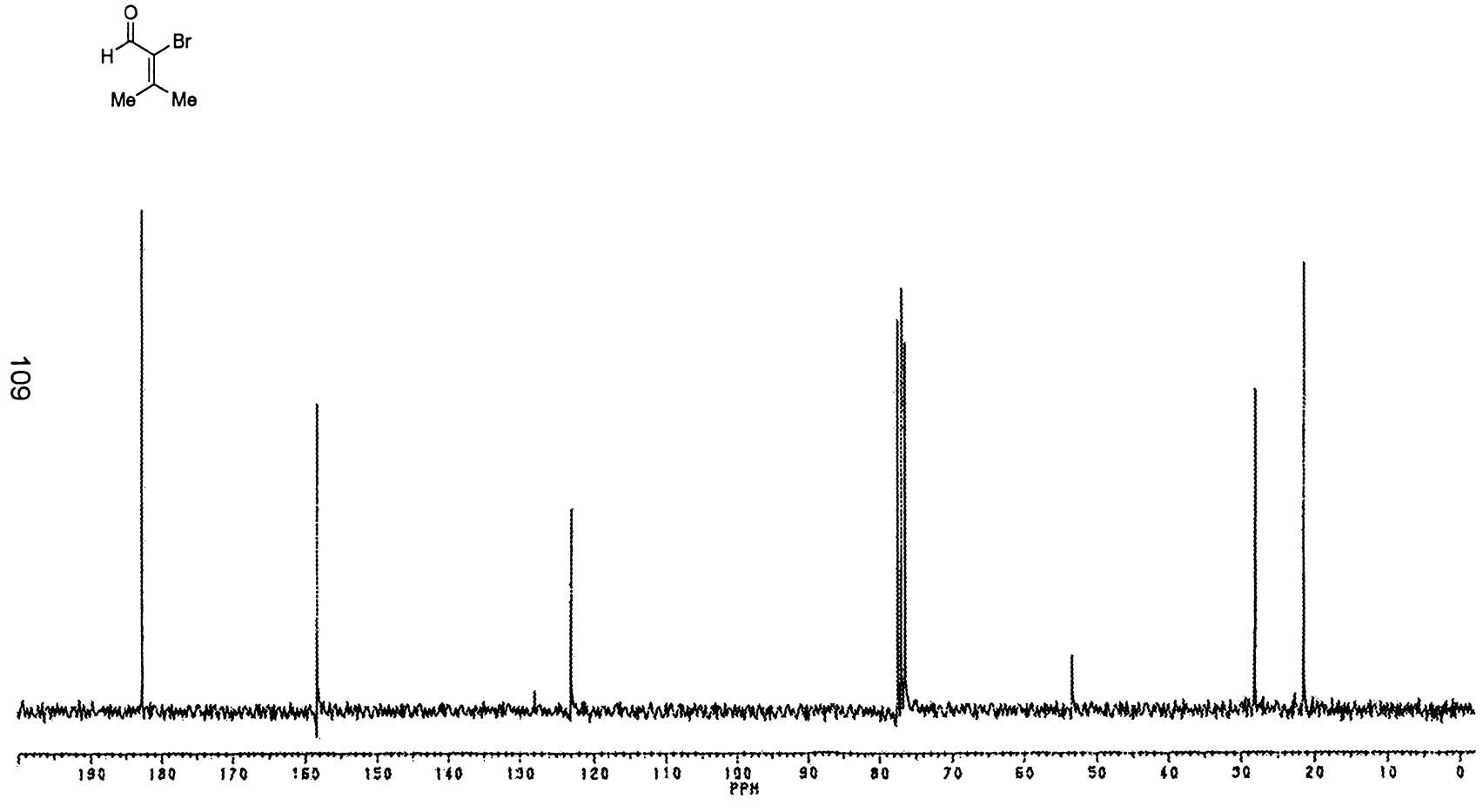
APPENDIX

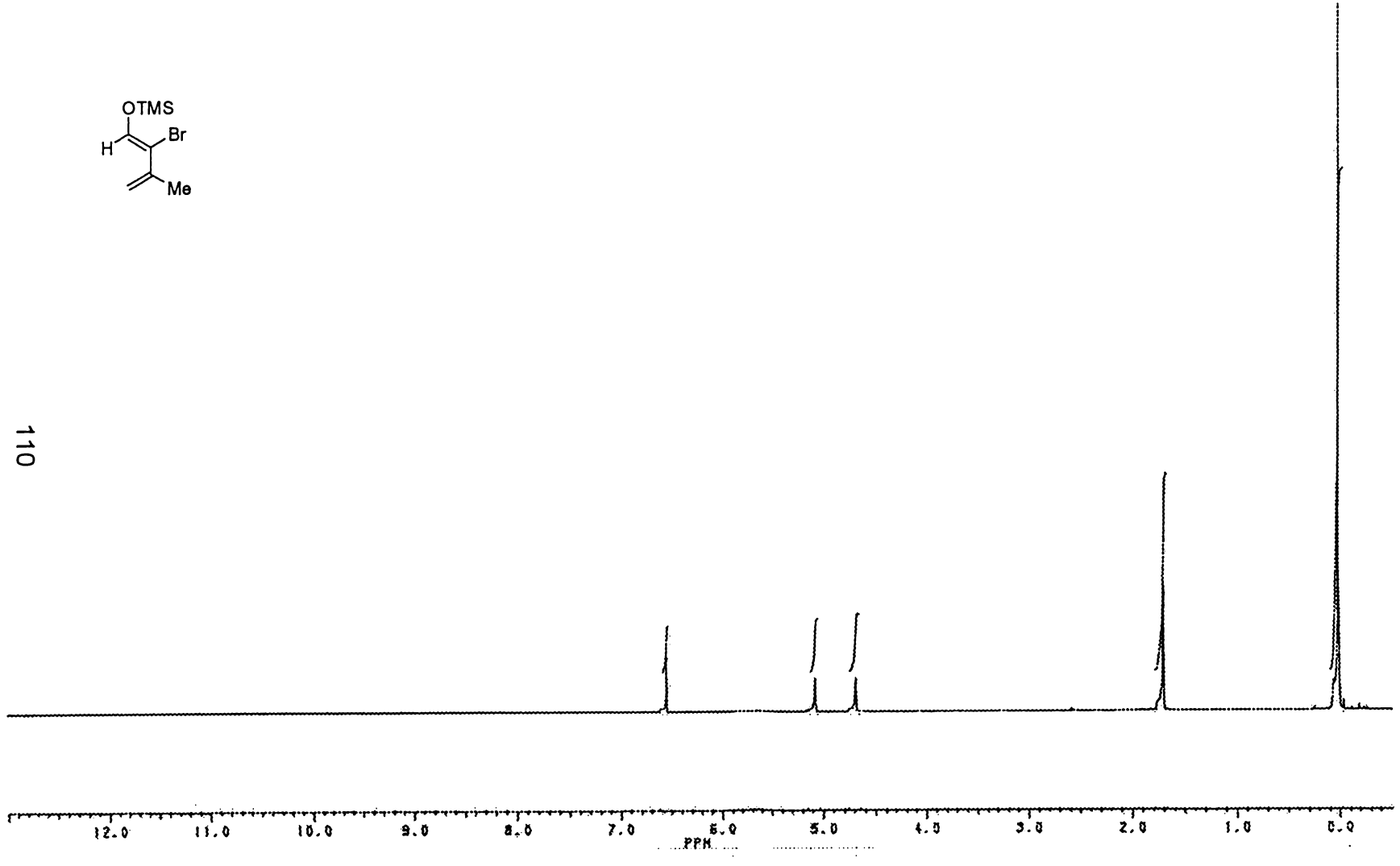
^{1}H and ^{13}C NMR Spectra for Intermediate and Target Compounds



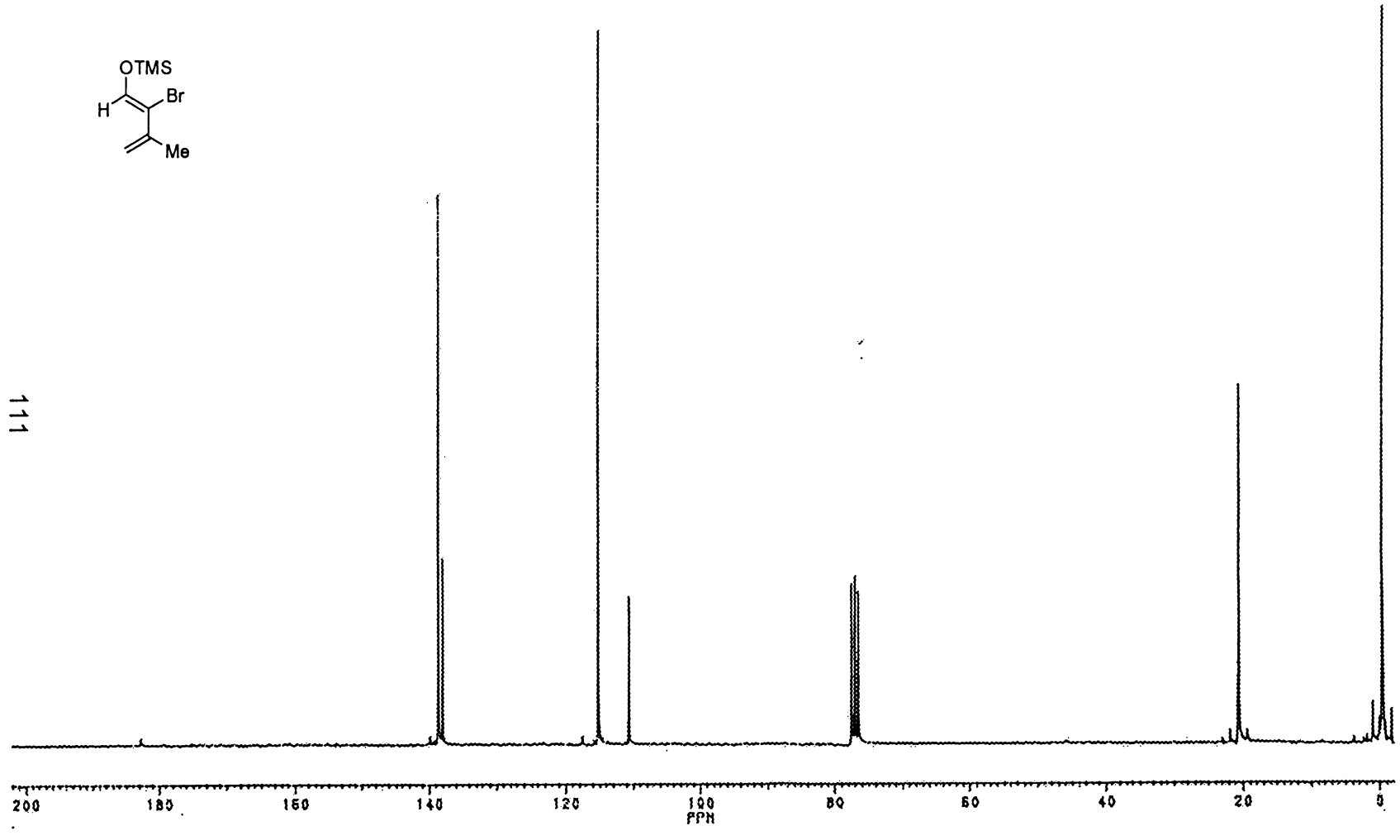
^{1}H NMR Spectrum (250 MHz, $CDCl_3$) of 2-Bromo-3-methyl-2-butenal (**30**).



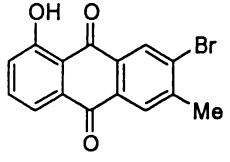
^{13}C NMR Spectrum (63 MHz, $CDCl_3$) of 2-Bromo-3-methyl-2-butenal (**30**).

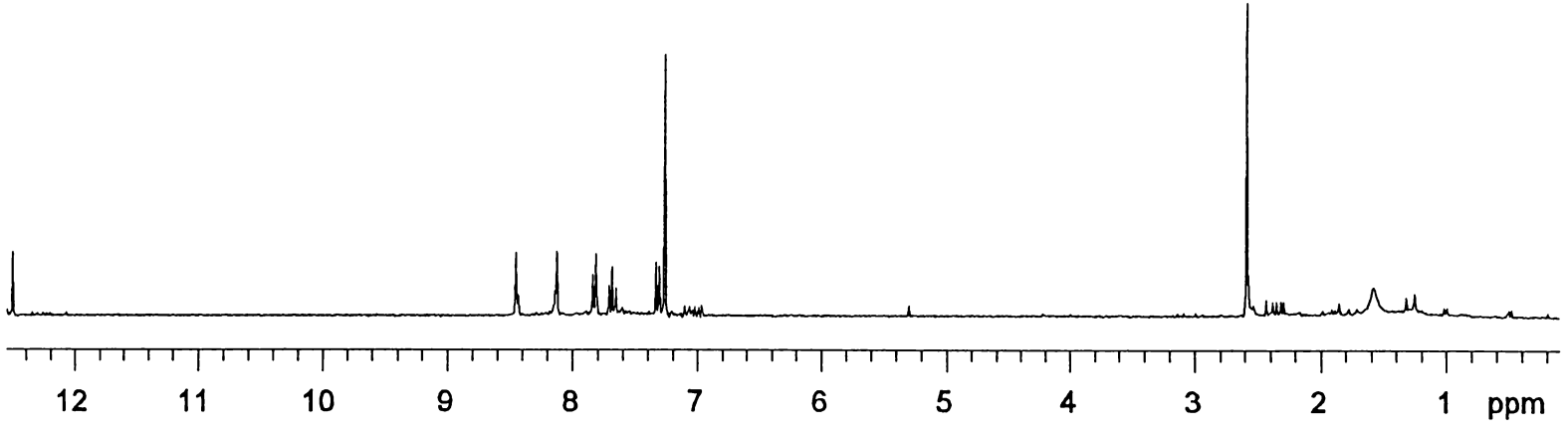


^{1}H NMR Spectrum (250 MHz, $CDCl_3$) of 2-Bromo-3-methyl-1-trimethylsilyloxy-1,3-butadiene (**31**).

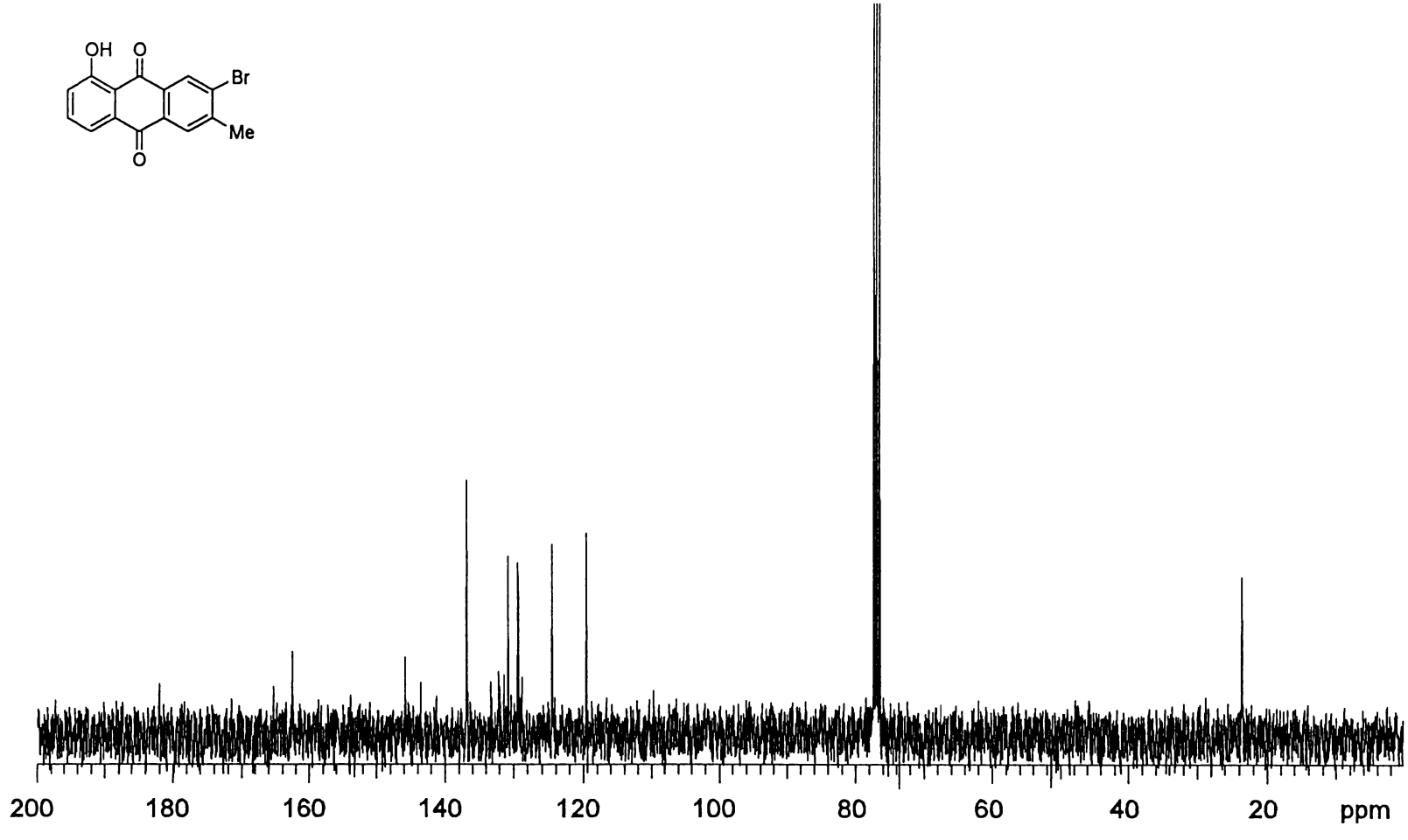


^{13}C NMR Spectrum (63 MHz, $CDCl_3$) of 2-Bromo-3-methyl-1-trimethylsilyloxy-1,3-butadiene (**31**).

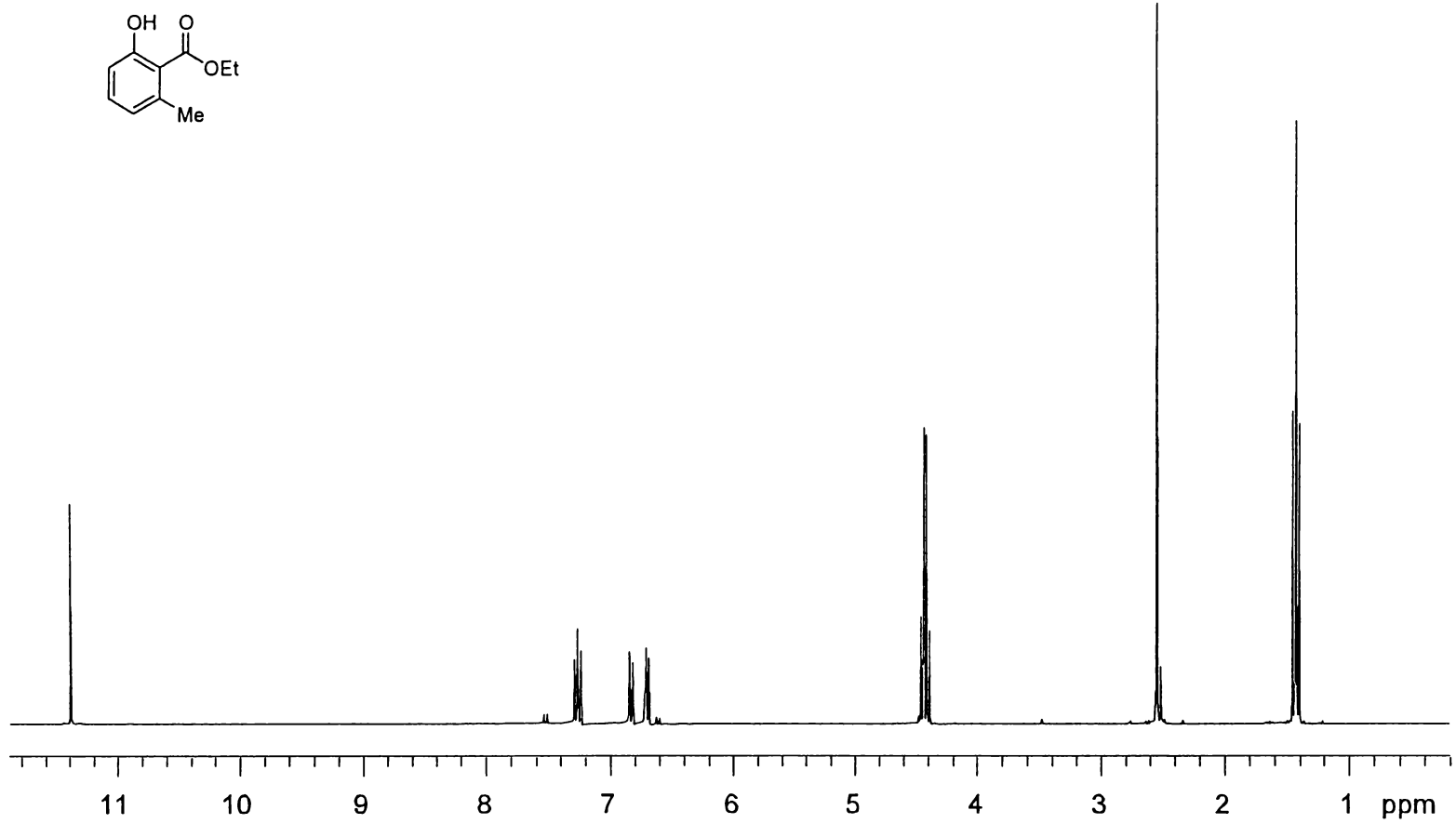




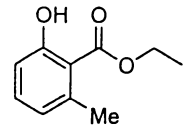
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 7-Bromo-1-hydroxy-6-methylanthraquinone (**35**).

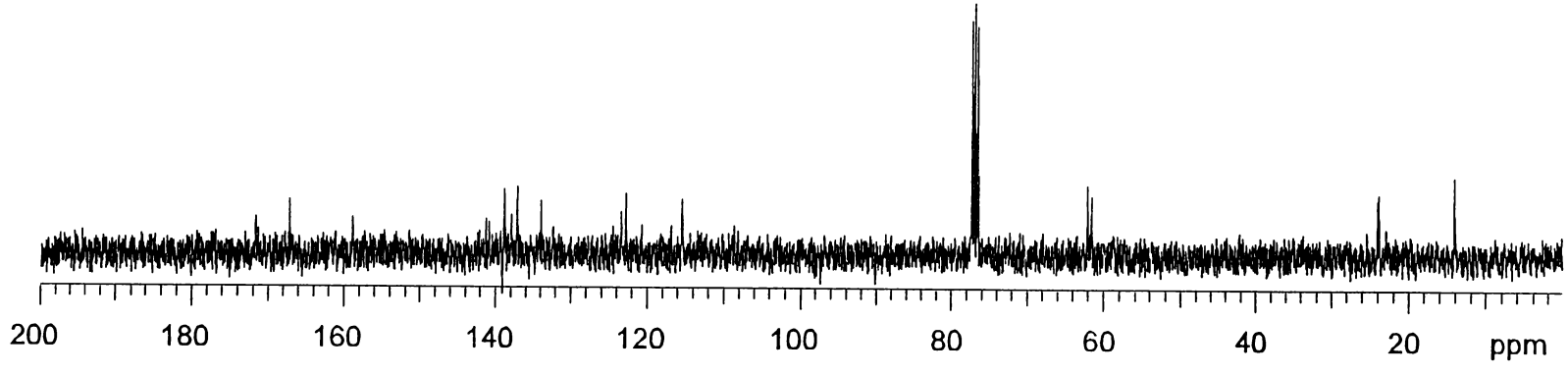


^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 7-Bromo-1-hydroxy-6-methylanthraquinone (**35**).

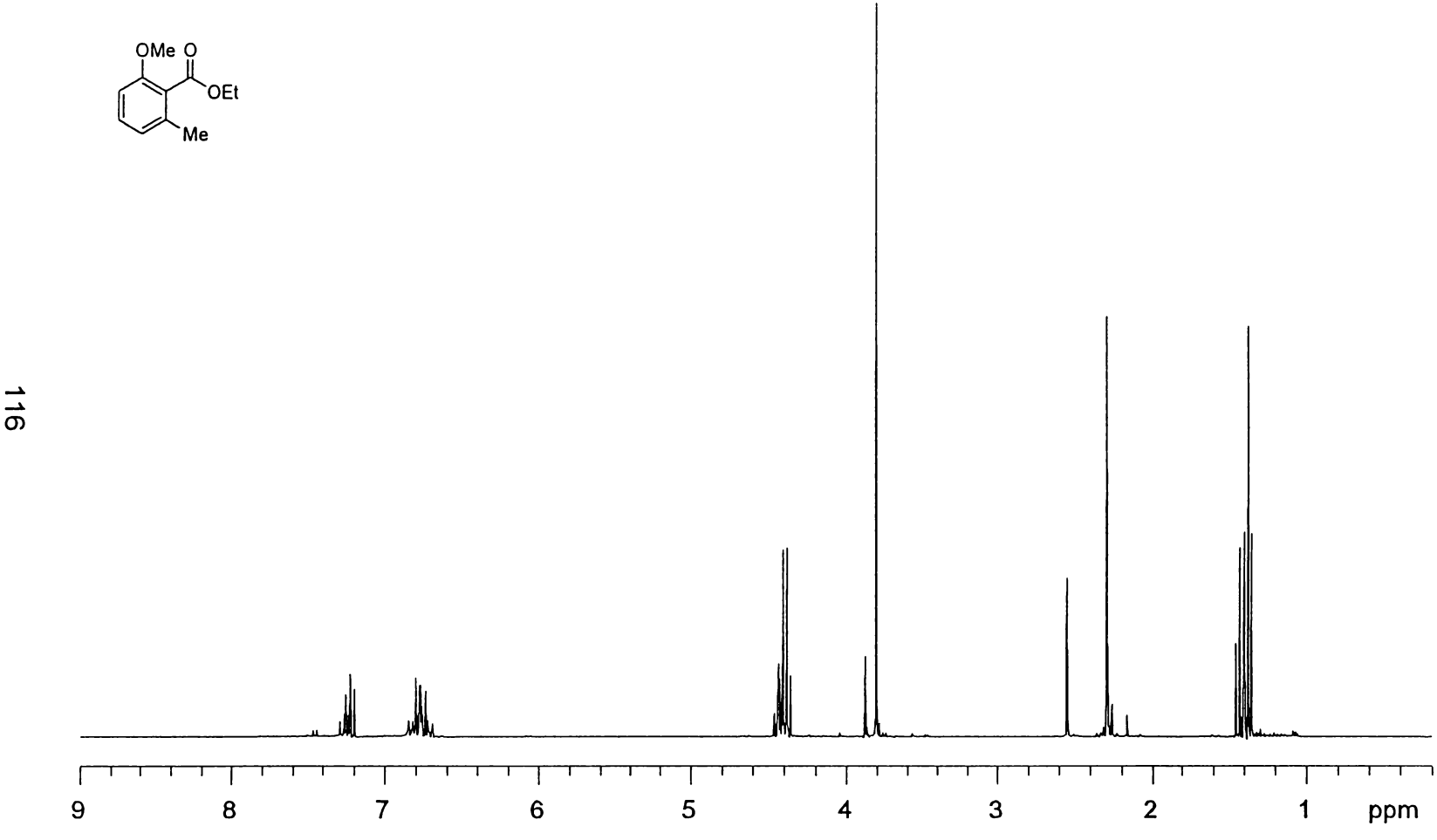


^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of Ethyl 2-Hydroxy-6-methylbenzoate (**17**).

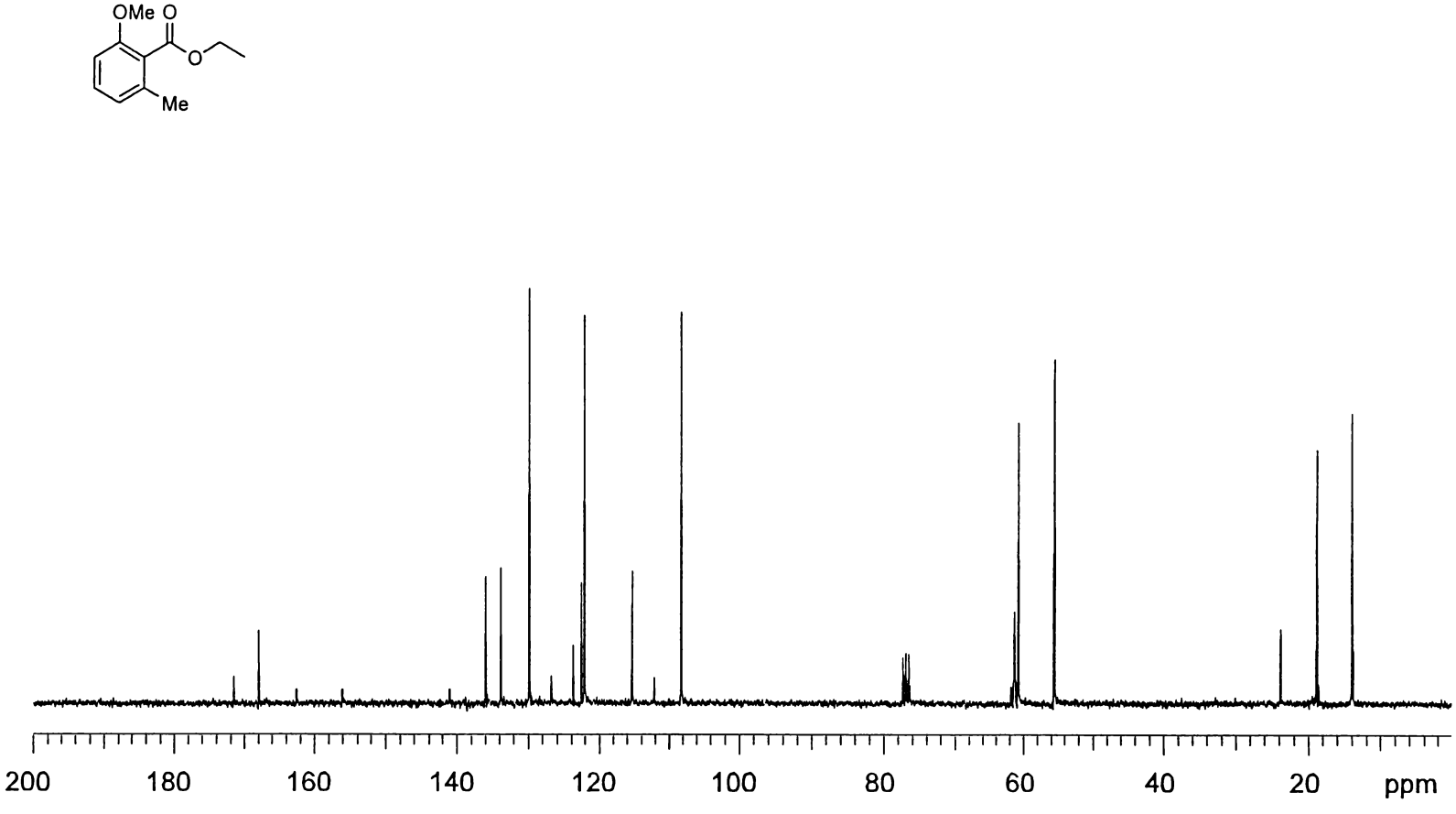




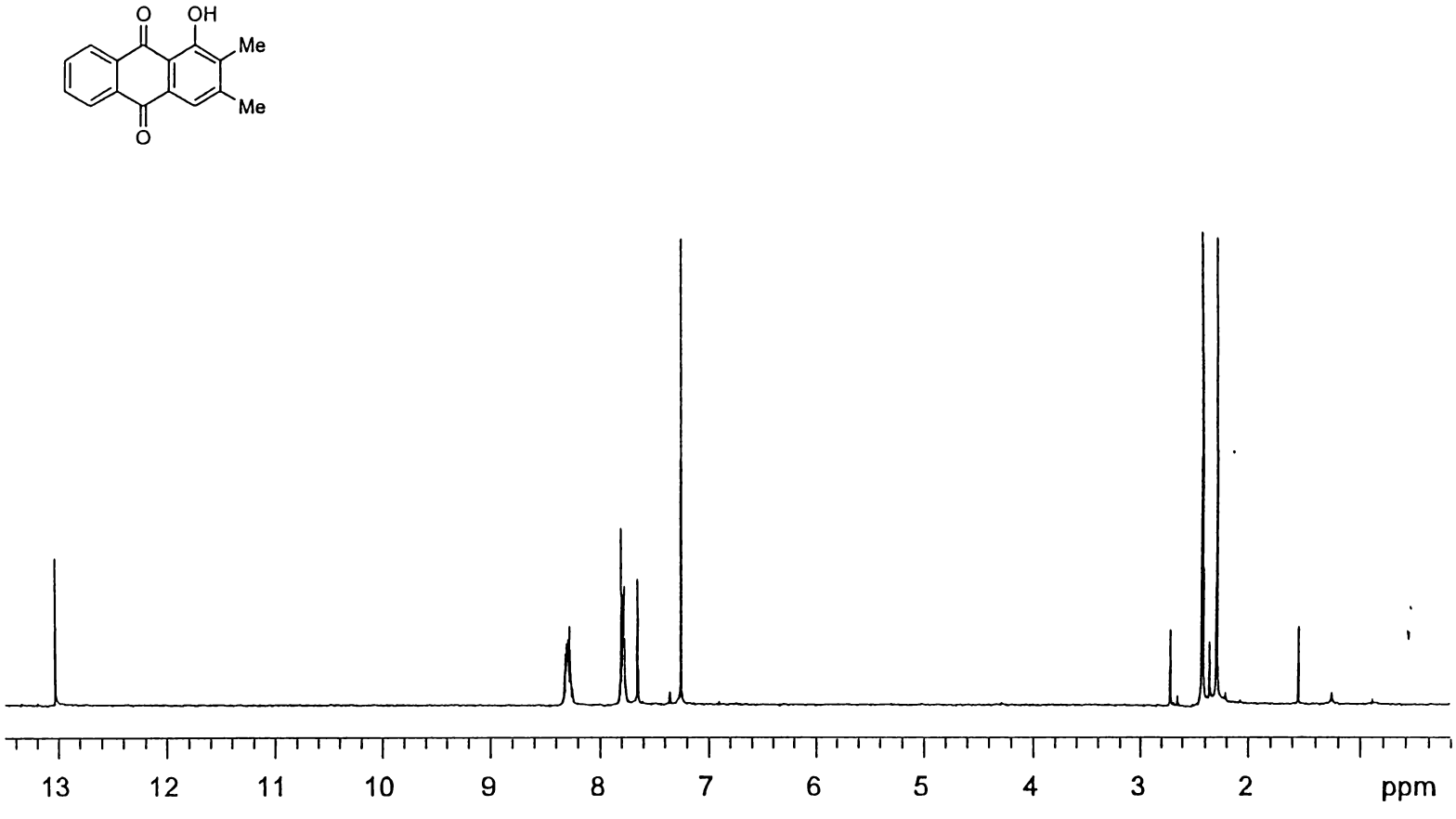
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of Ethyl 2-Hydroxy-6-methylbenzoate (**17**).



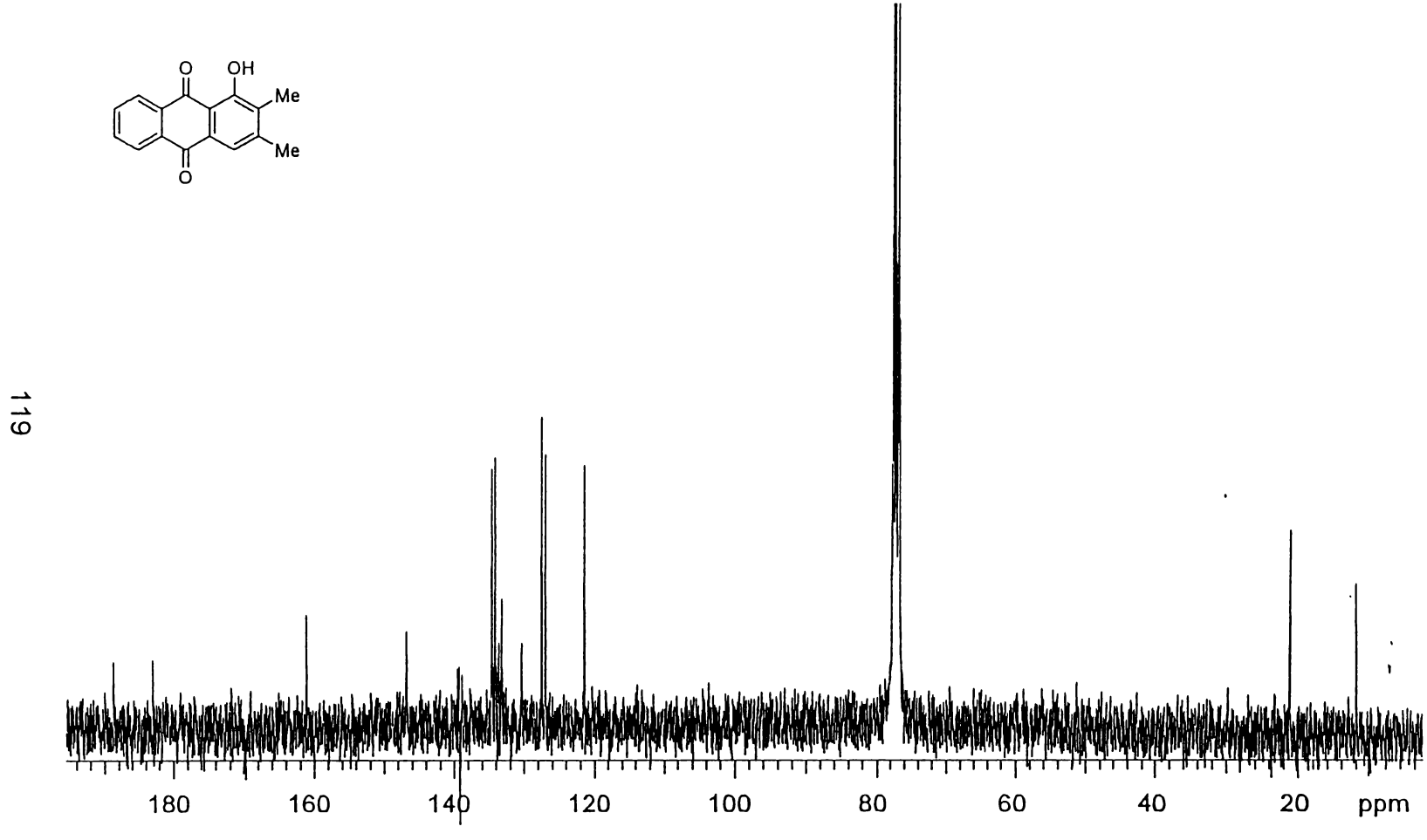
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of Ethyl 2-Methoxy-6-methyl-benzoate (**18**).



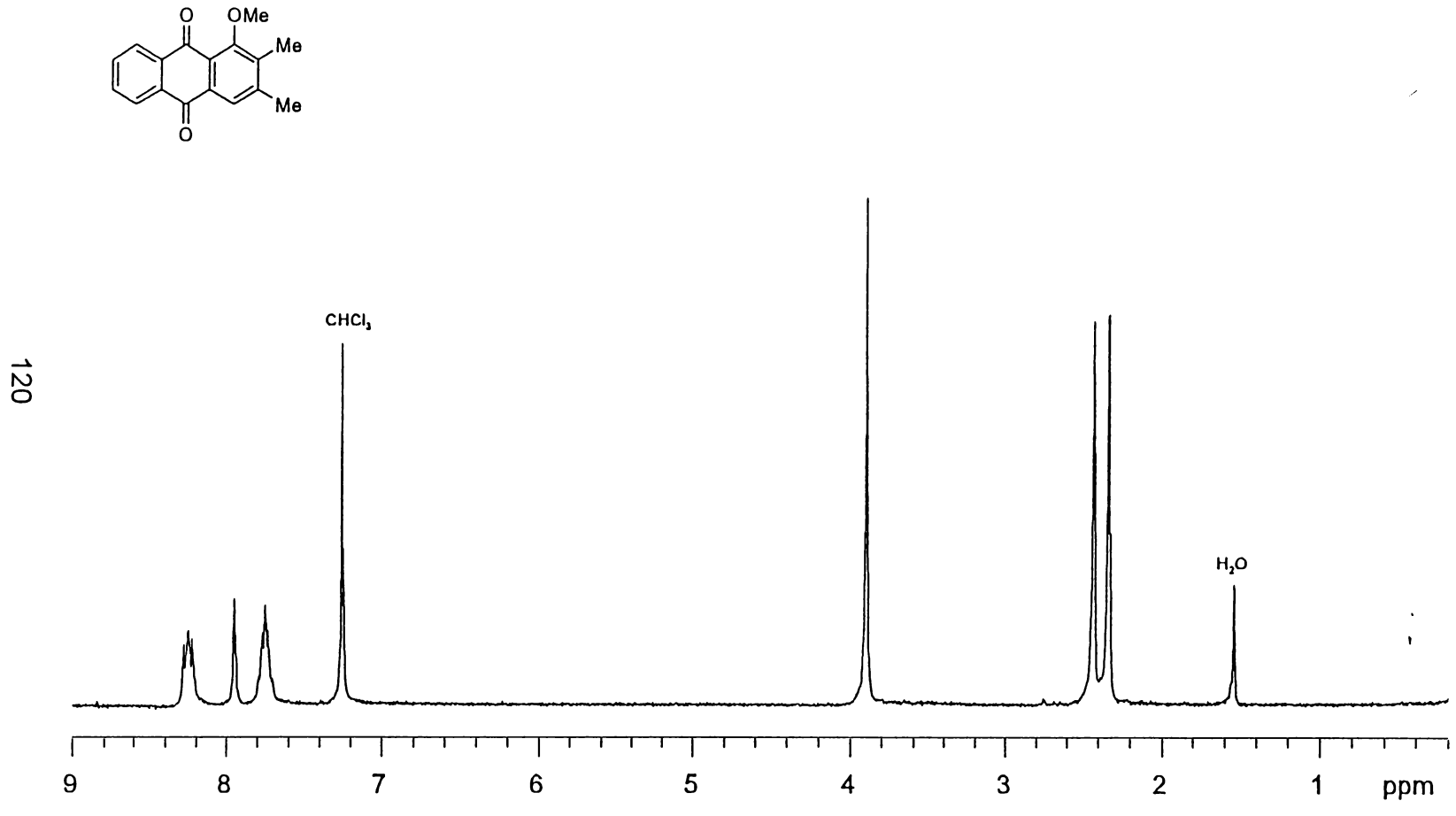
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of Ethyl 2-Methoxy-6-methylbenzoate (**18**).



^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-Hydroxy-2,3-dimethylanthraquinone (**36**).

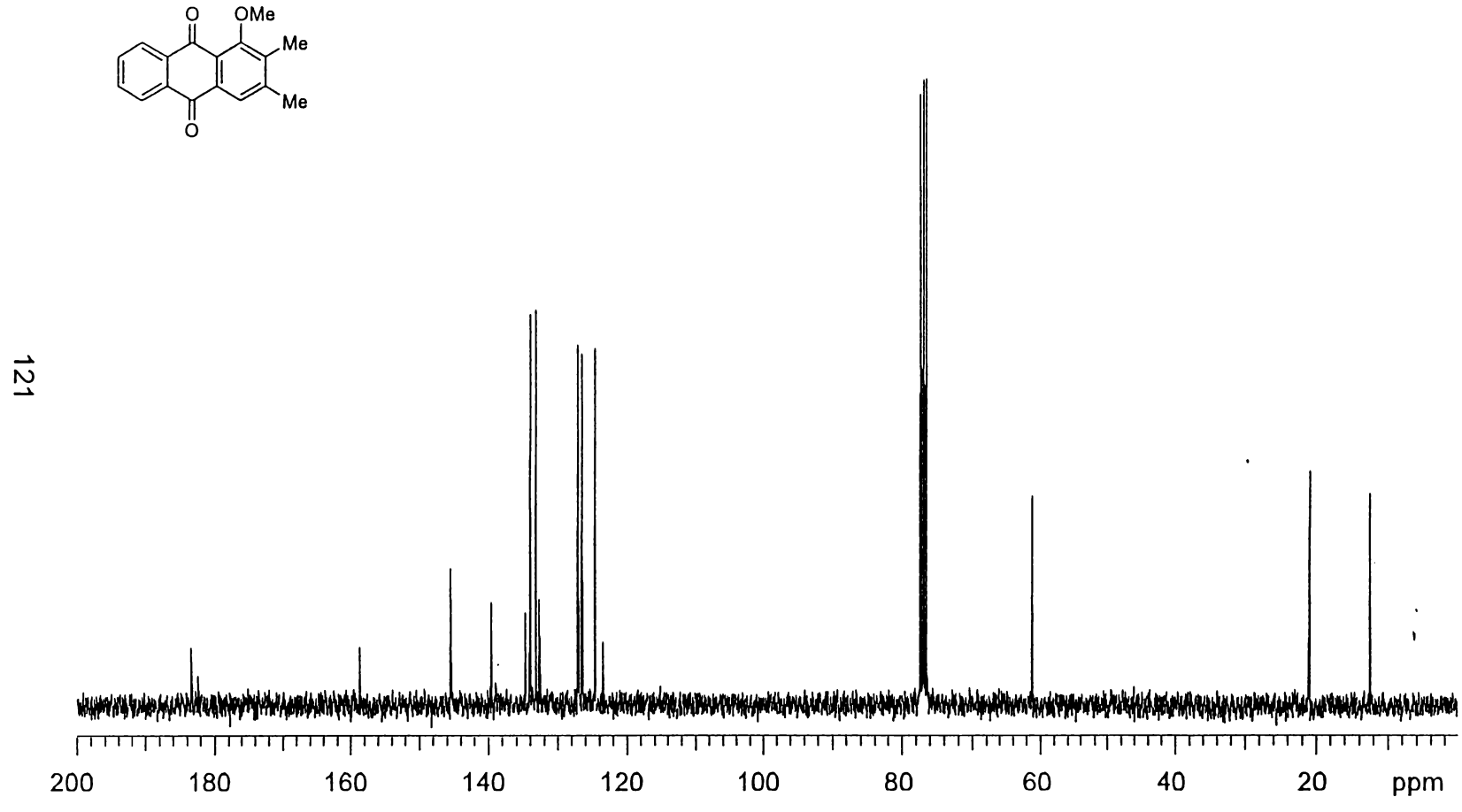


^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 1-Hydroxy-2,3-dimethylanthraquinone (**36**).

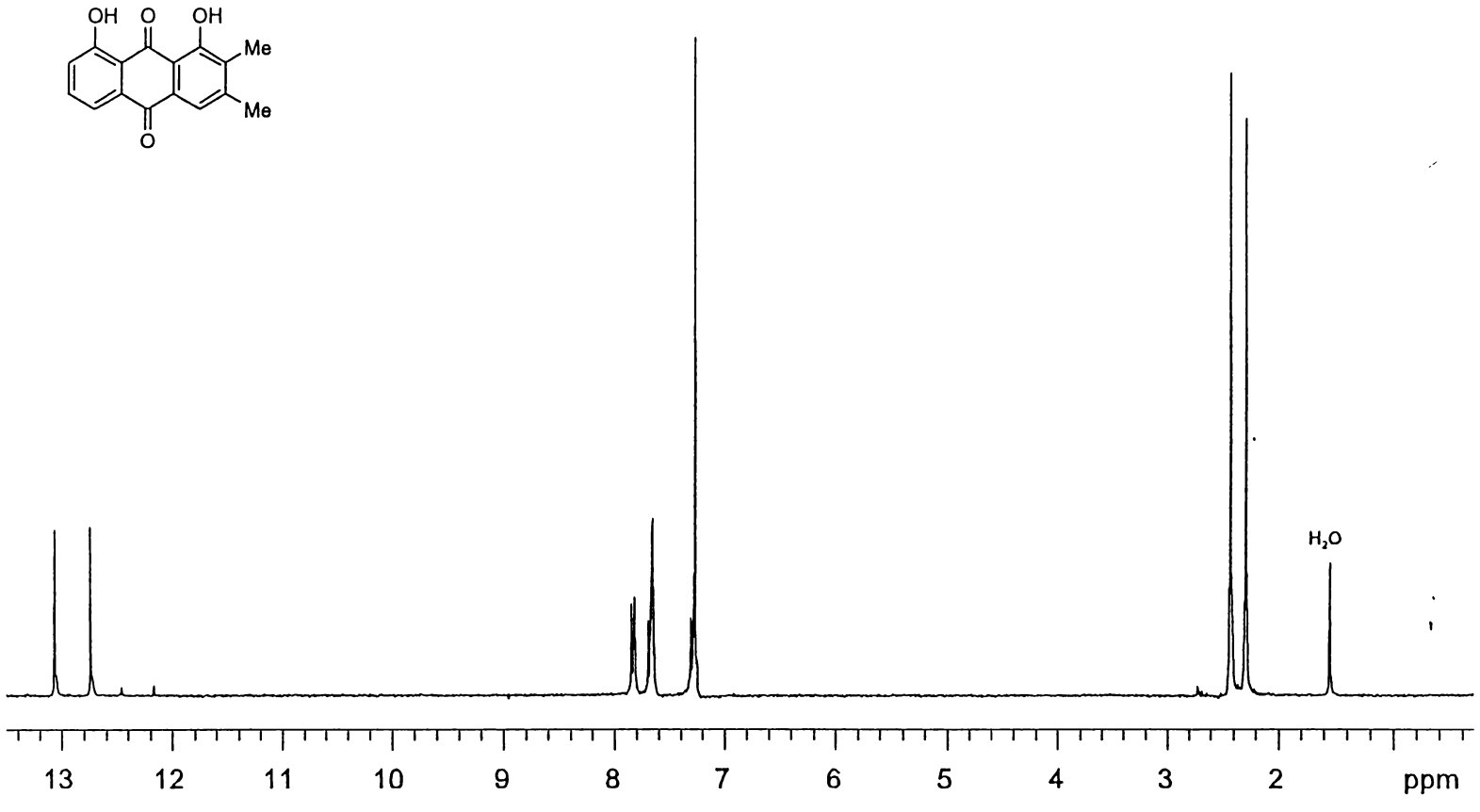


120

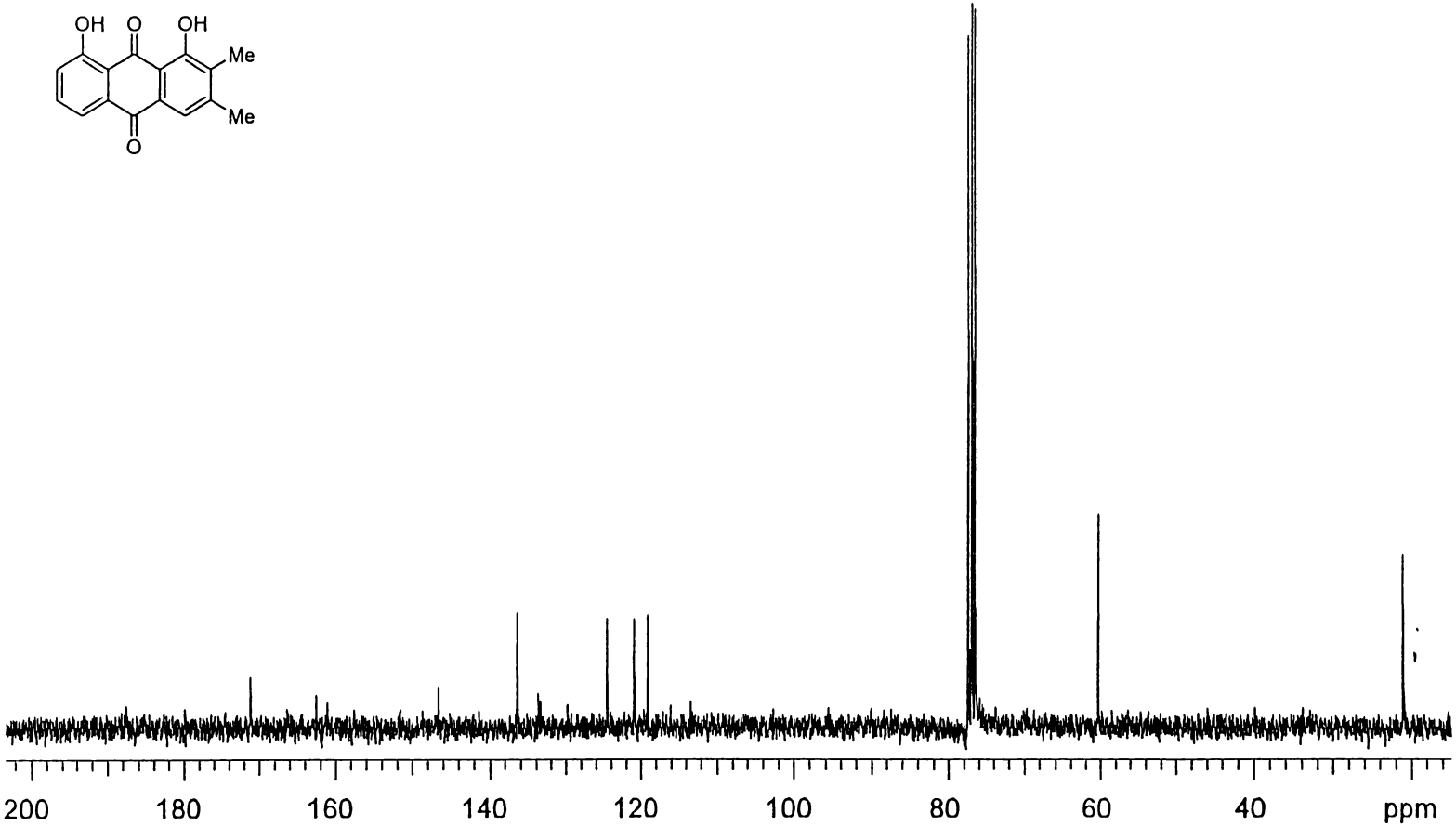
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-Methoxy-2,3-dimethylanthraqunone (**46**).



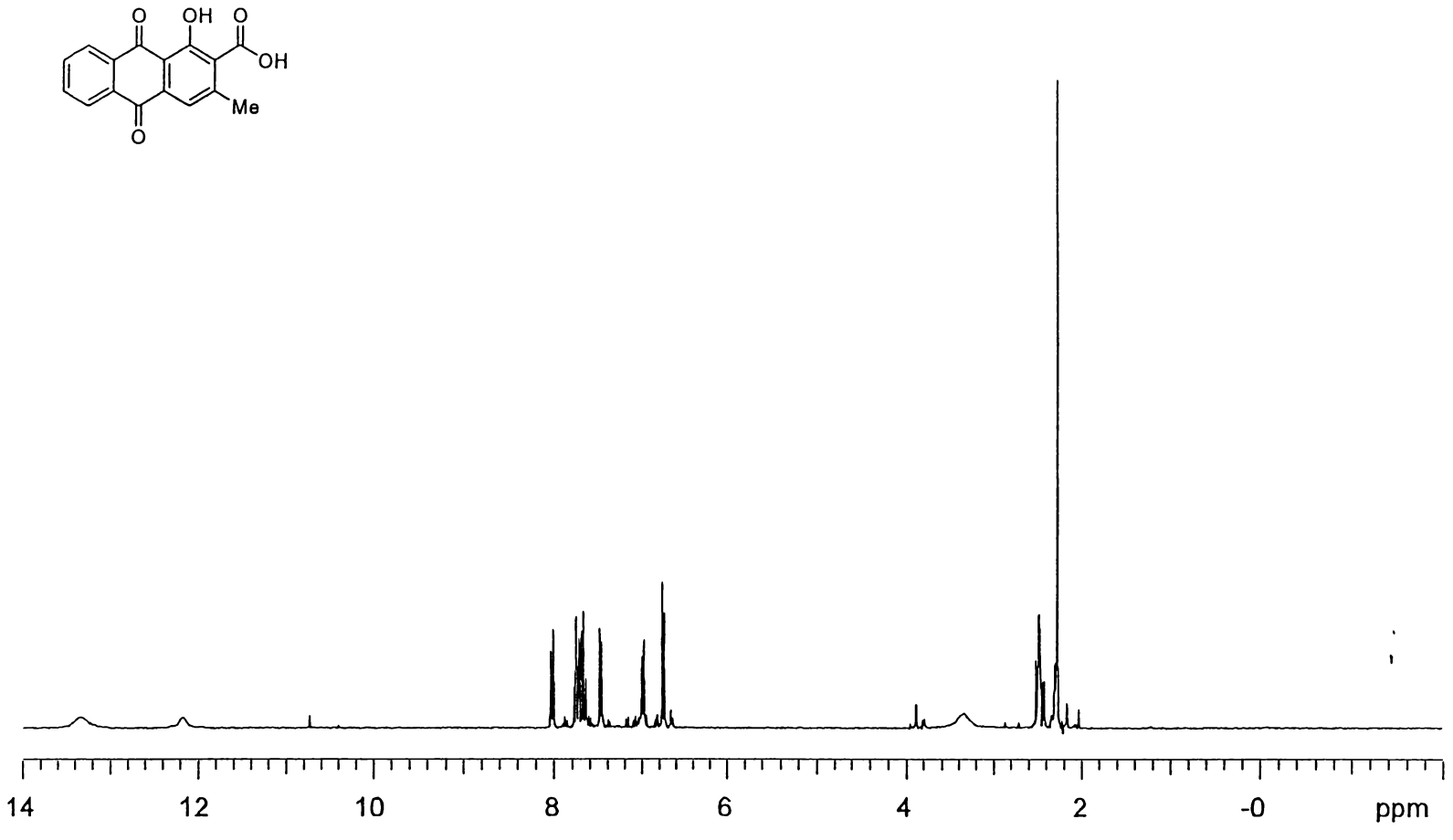
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 1-Methoxy-2,3-dimethylanthraquinone (**46**).



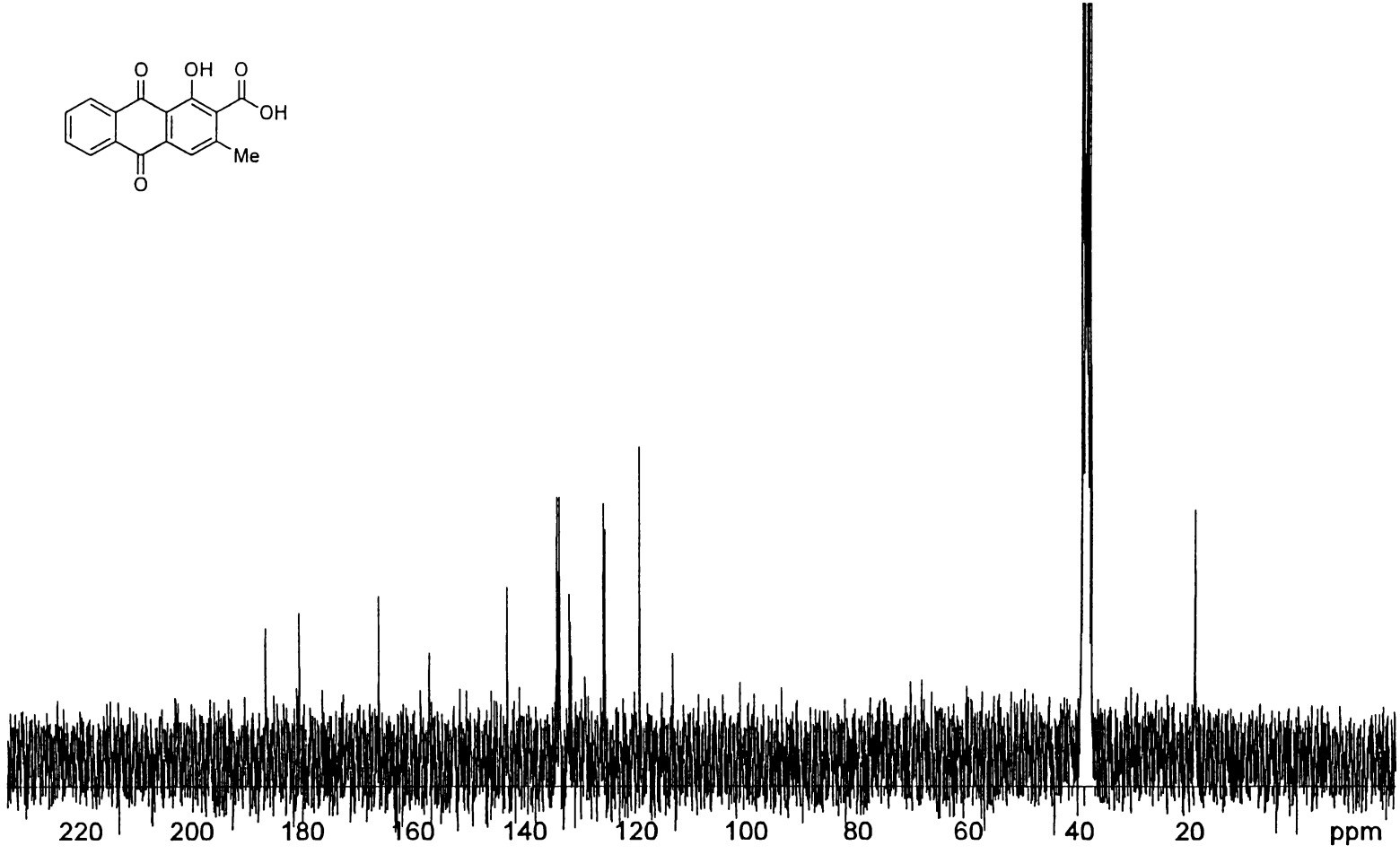
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1,8-Dihydroxy-2,3-dimethylanthraquinone (**37**).



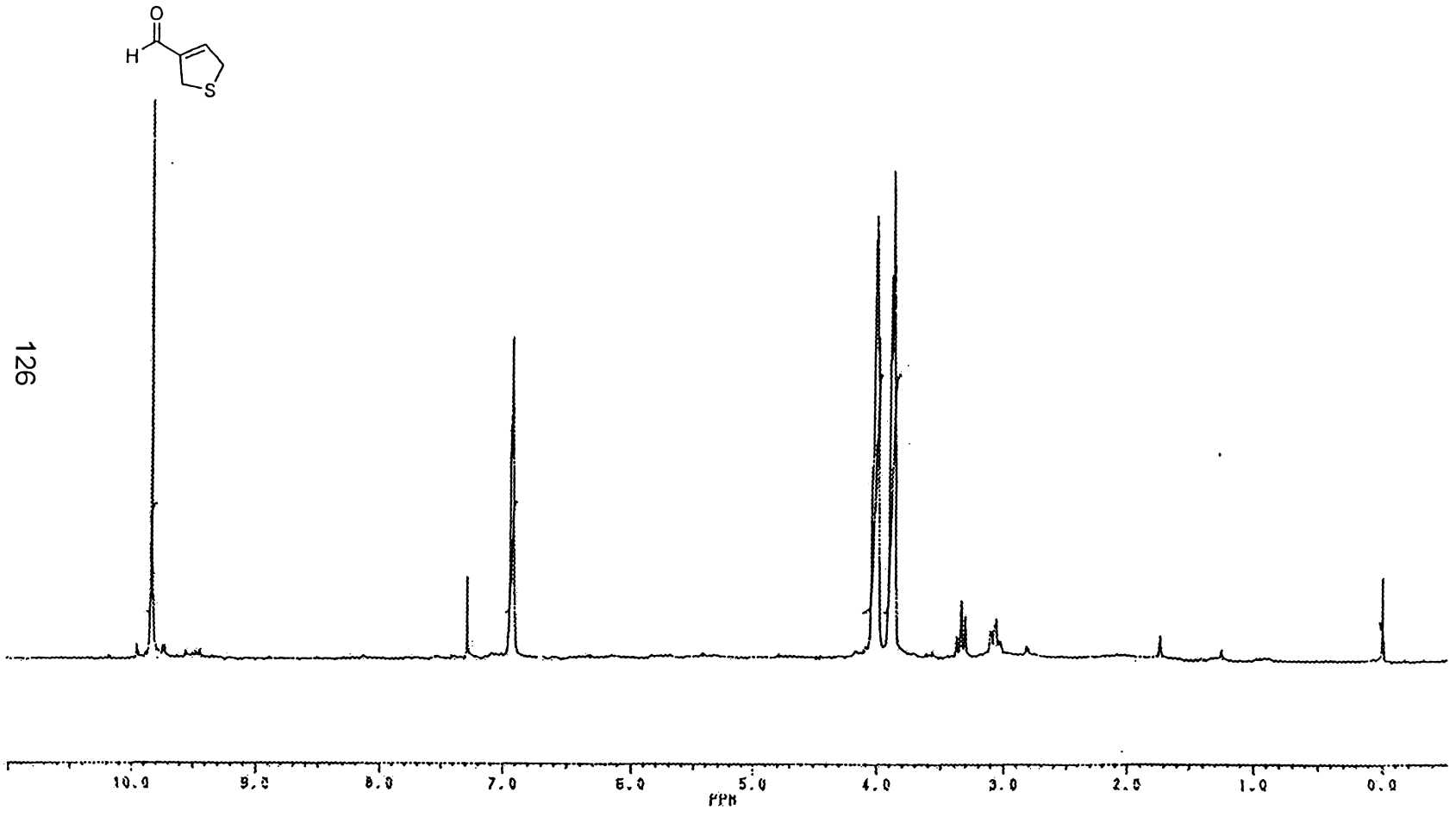
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 1,8-Dihydroxy-2,3-dimethylanthraquinone (**37**).



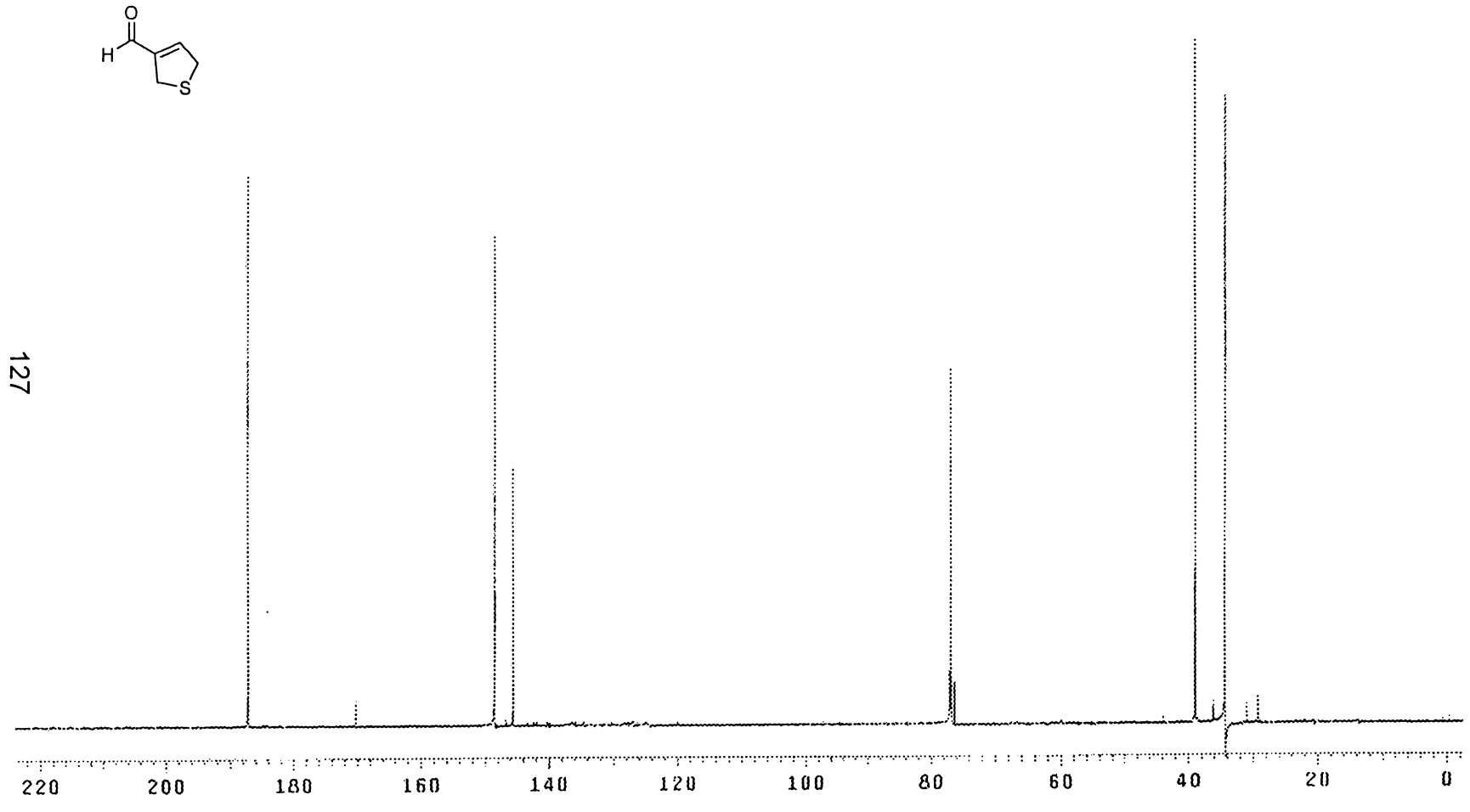
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-Hydroxy-3-methylanthraquinone-2-carboxylic Acid (**45**).



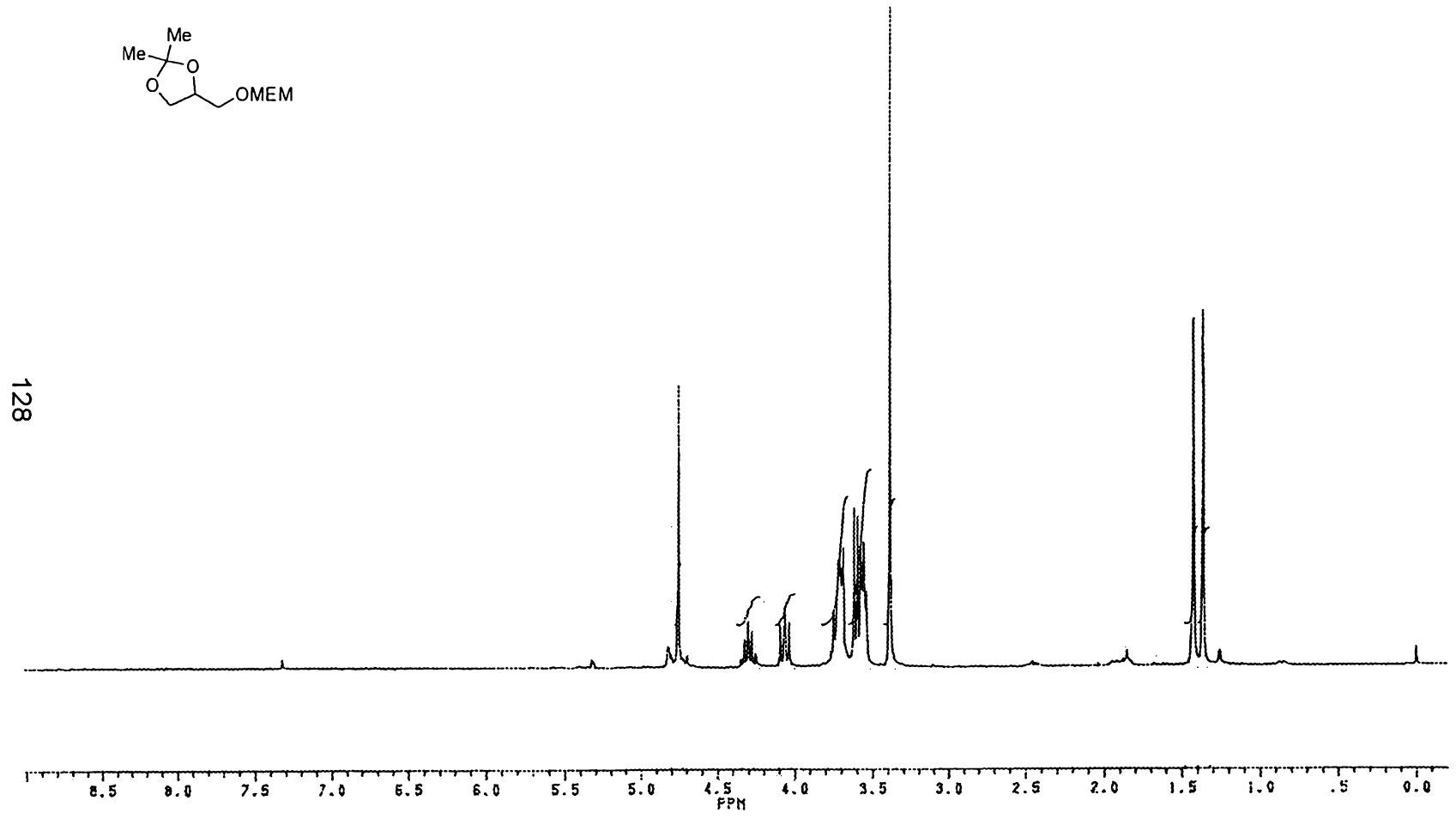
^{13}C NMR Spectrum (75 MHz, DMSO–d_6) of 1-Hydroxy-3-methylanthraquinone-2-carboxylic Acid (**45**).



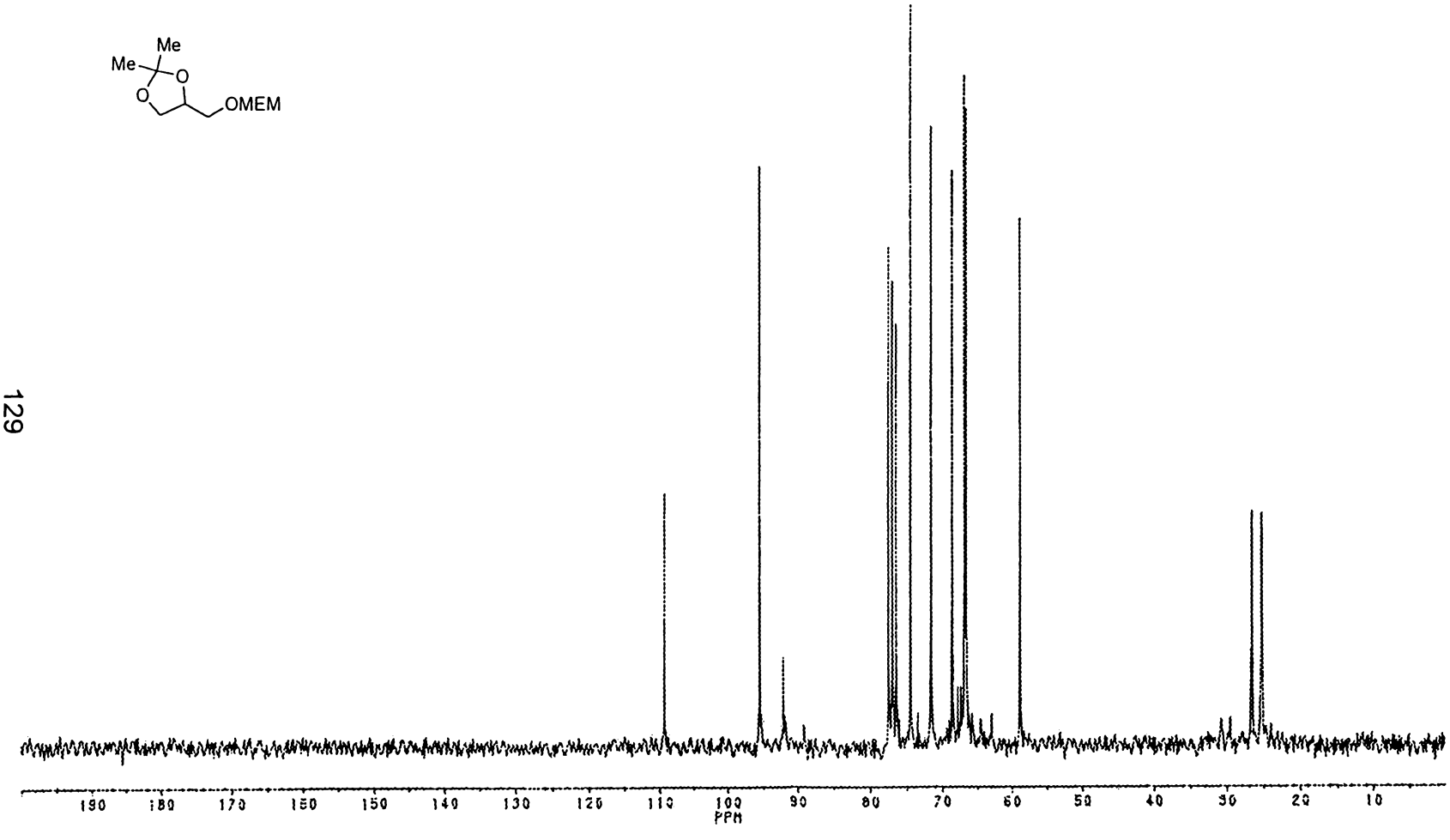
^{1}H NMR Spectrum (250 MHz, $CDCl_3$) of 2,5-Dihydro-thiophene-3-carbaldehyde (**48**).



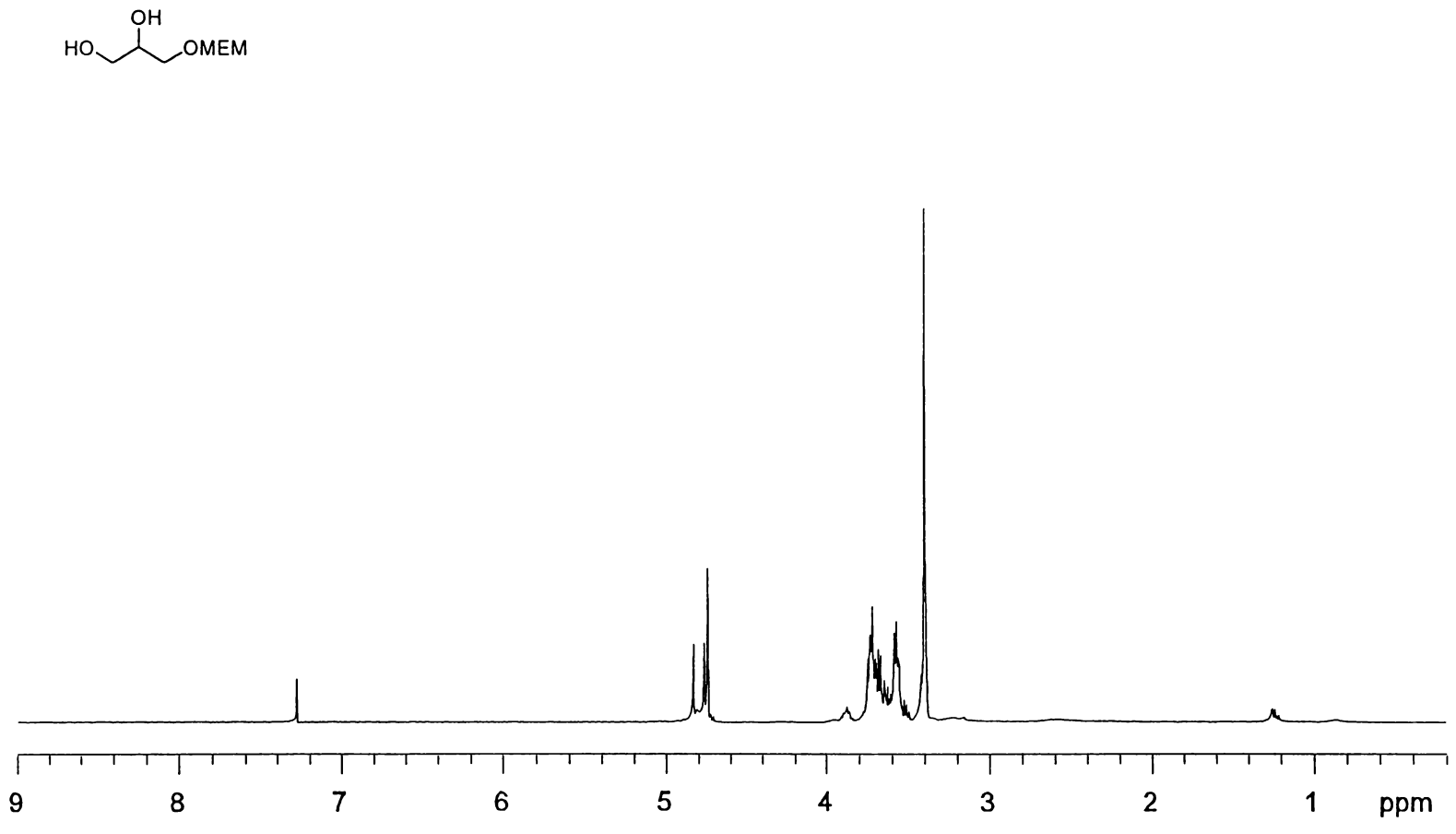
^{13}C NMR Spectrum (63 MHz, $CDCl_3$) of 2,5-Dihydro-thiophene-3-carbaldehyde (**48**).



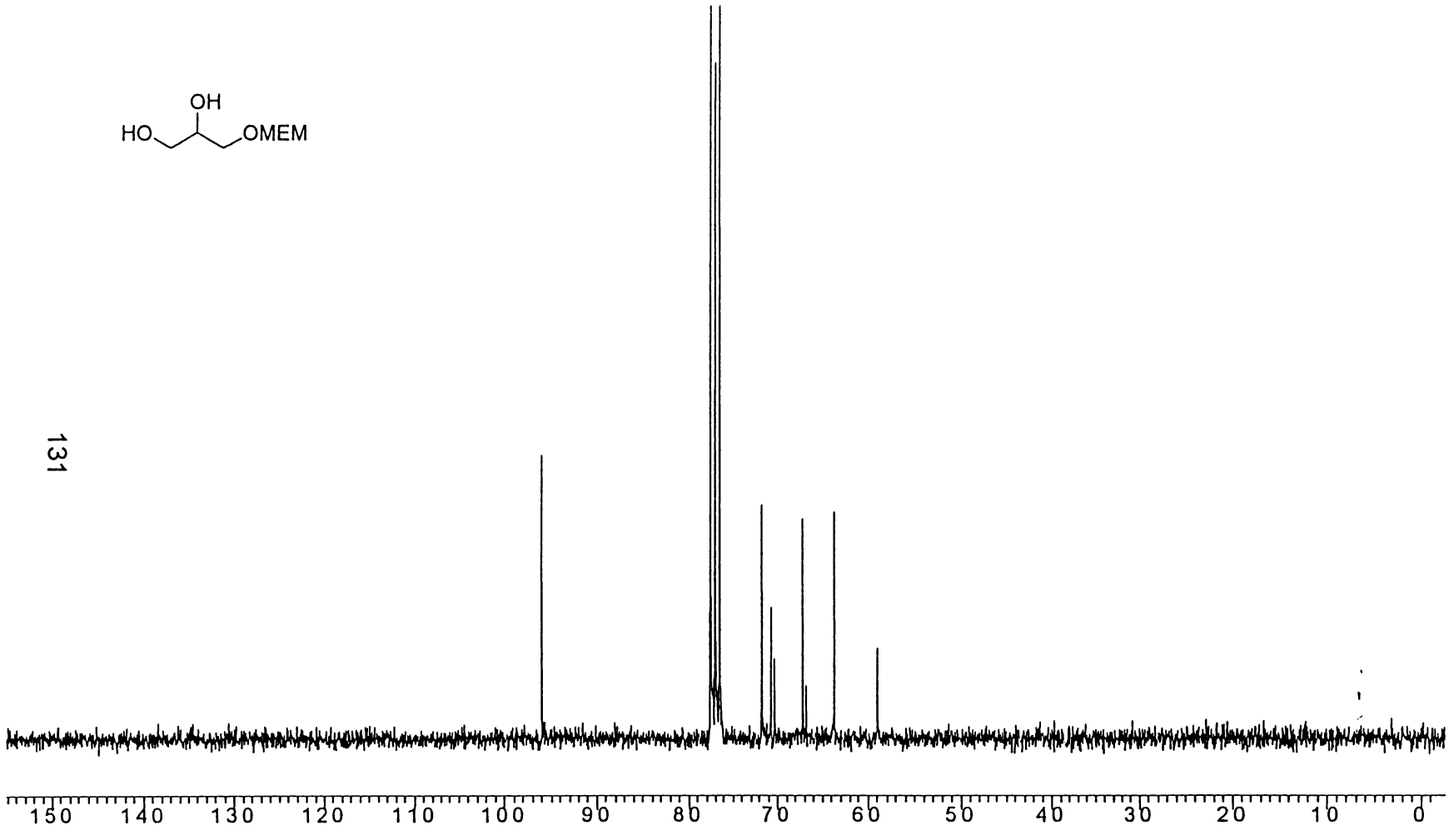
^{1}H NMR Spectrum (250 MHz, $CDCl_3$) of 4-(2-Methoxy-ethoxymethoxymethyl)-2,2-dimethyl-[1,3]dioxolane (**52**).



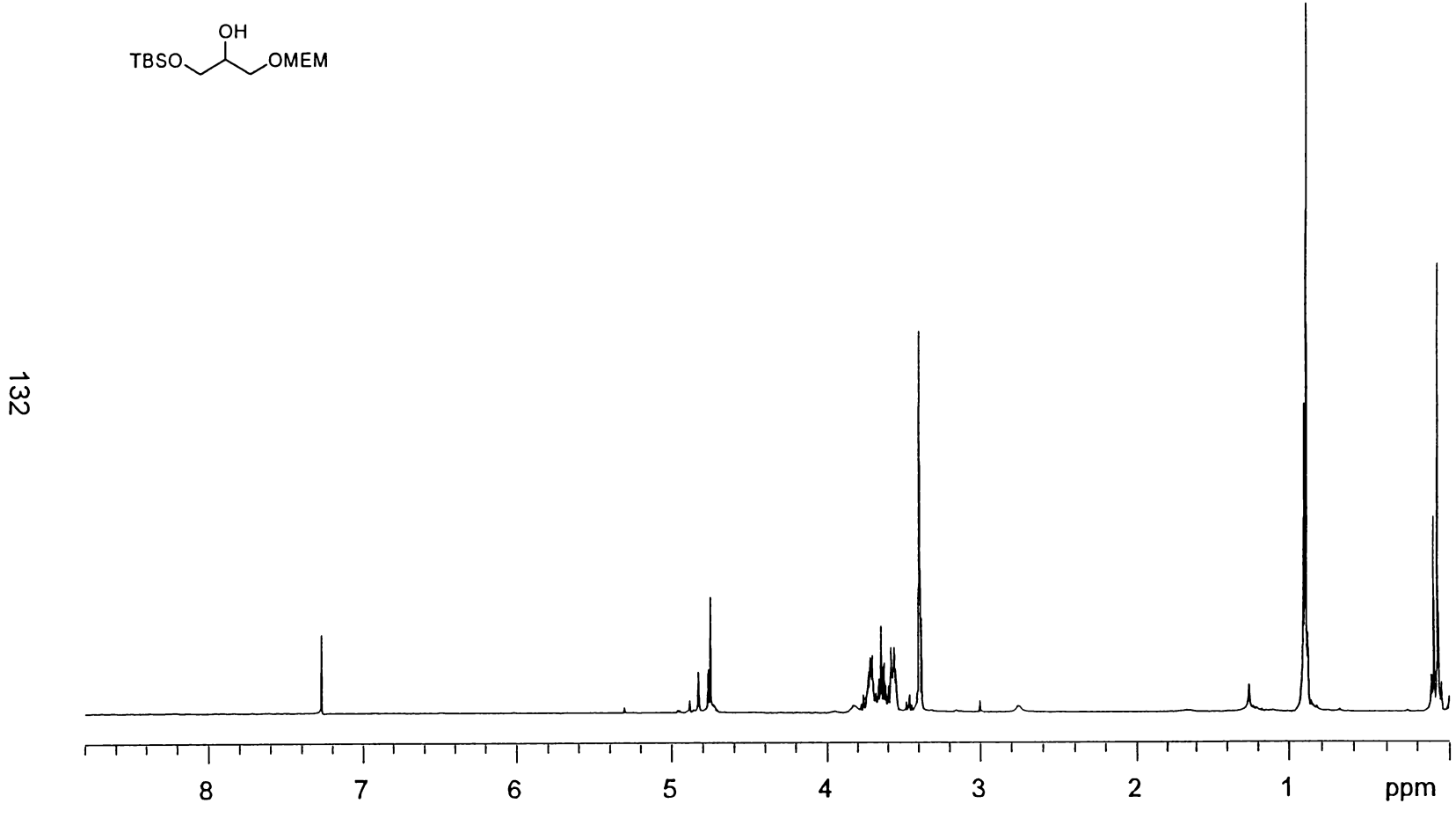
^{13}C NMR Spectrum (63 MHz, $CDCl_3$) of 4-(2-Methoxy-ethoxymethoxymethyl)-2,2-dimethyl-[1,3]dioxolane (**52**).



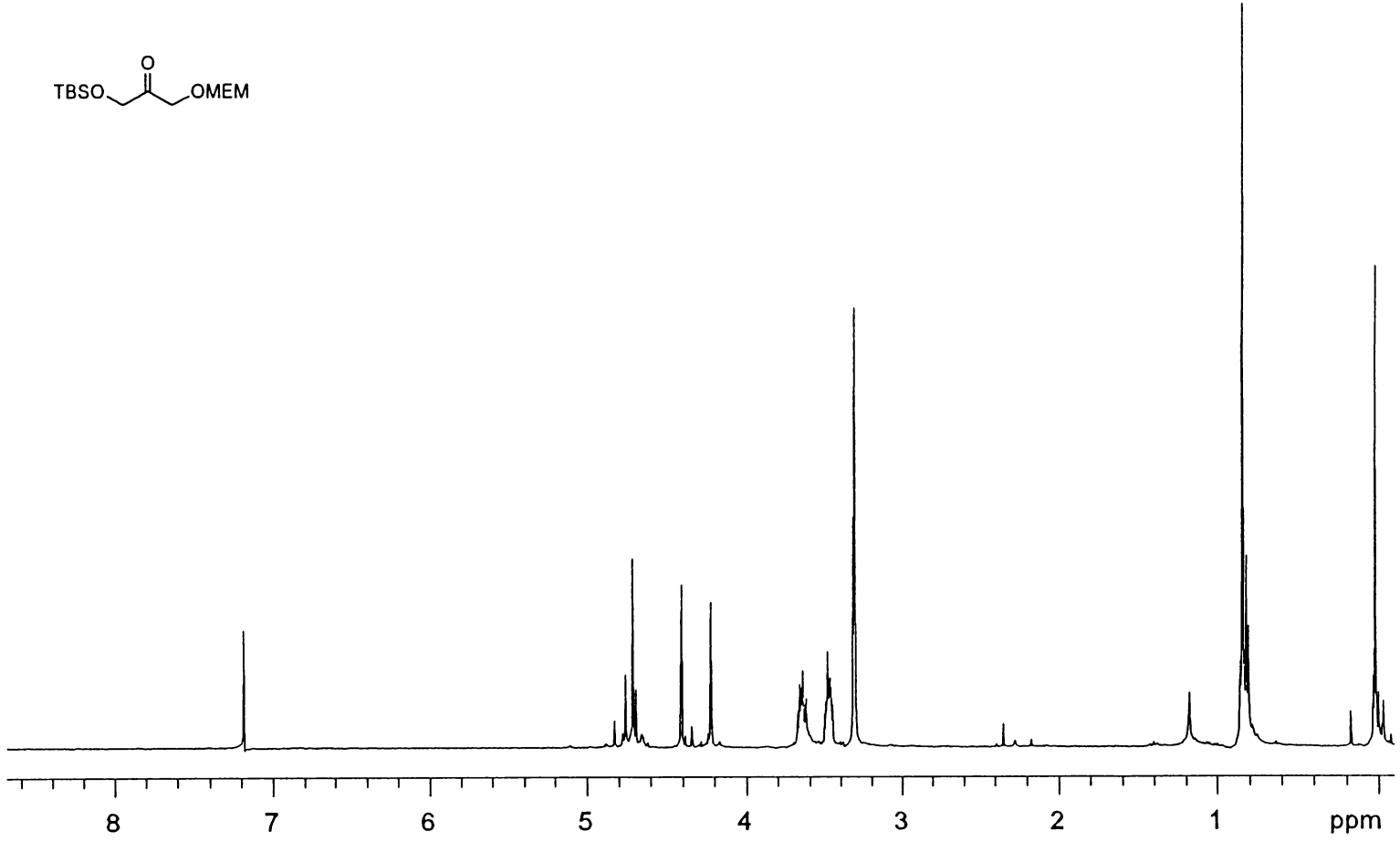
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 3-(2-Methoxy-ethoxymethoxy)-propane-1,2-diol (**53**).



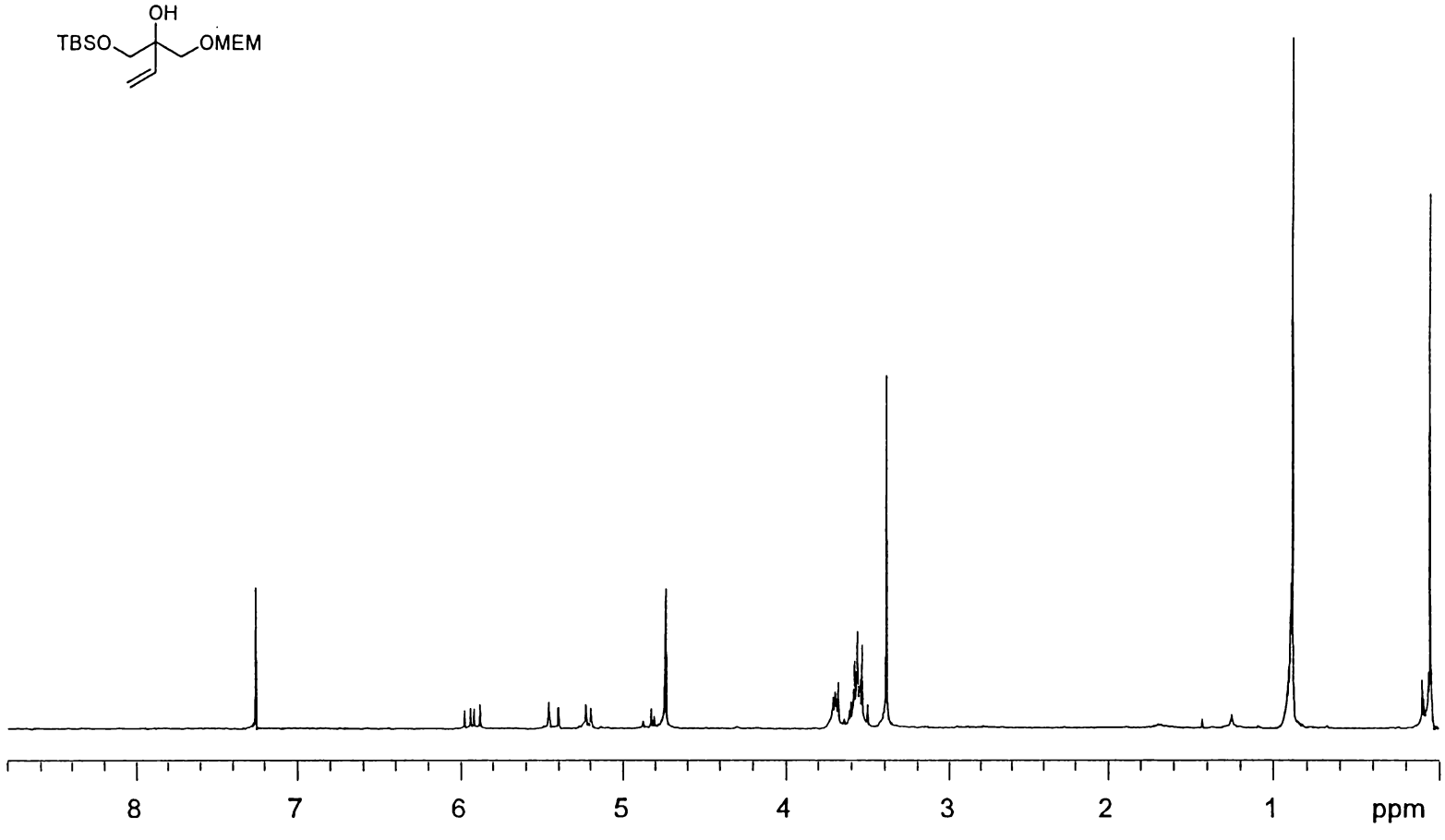
^{13}C NMR Spectrum (63 MHz, $CDCl_3$) of 3-(2-Methoxy-ethoxymethoxy)-propane-1,2-diol (**53**).



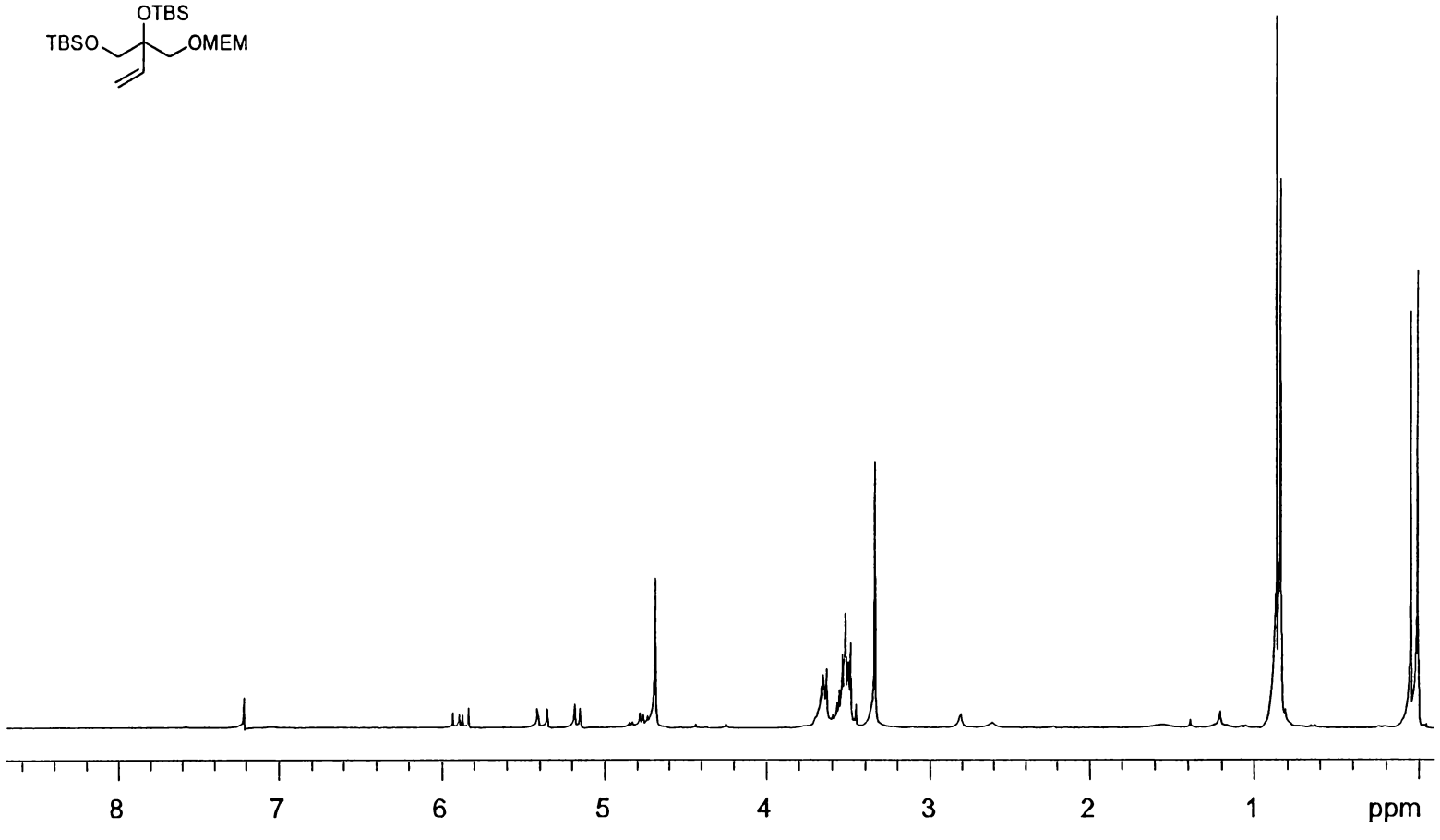
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-(*tert*-Butyldimethylsilyloxy)-3-(2-methoxy-ethoxymethoxy)-propan-2-ol (**54**).



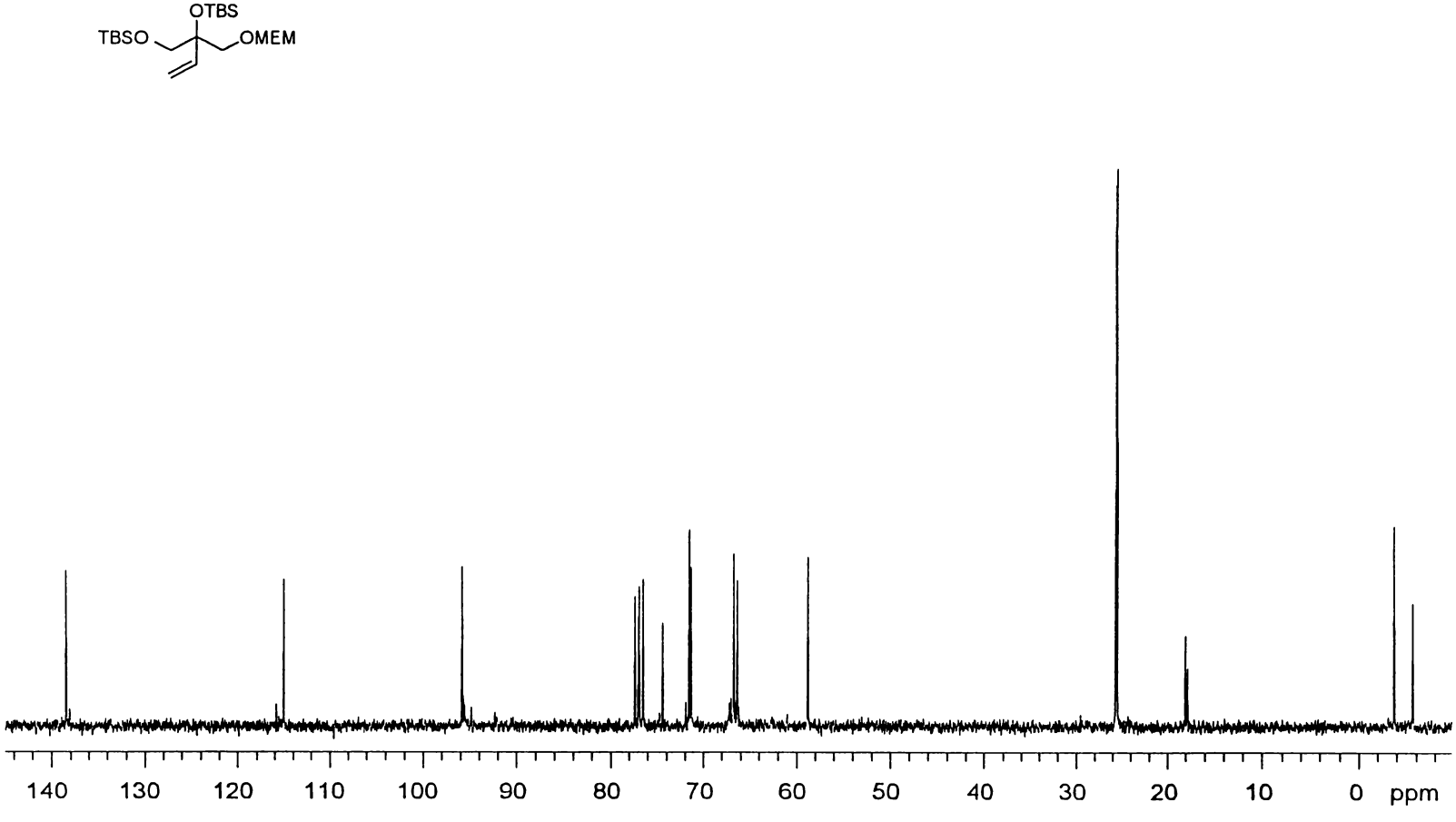
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
1-(*tert*-Butyldimethylsilyloxy)-3-(2-methoxy-ethoxymethoxy)-propan-2-one (**55**).



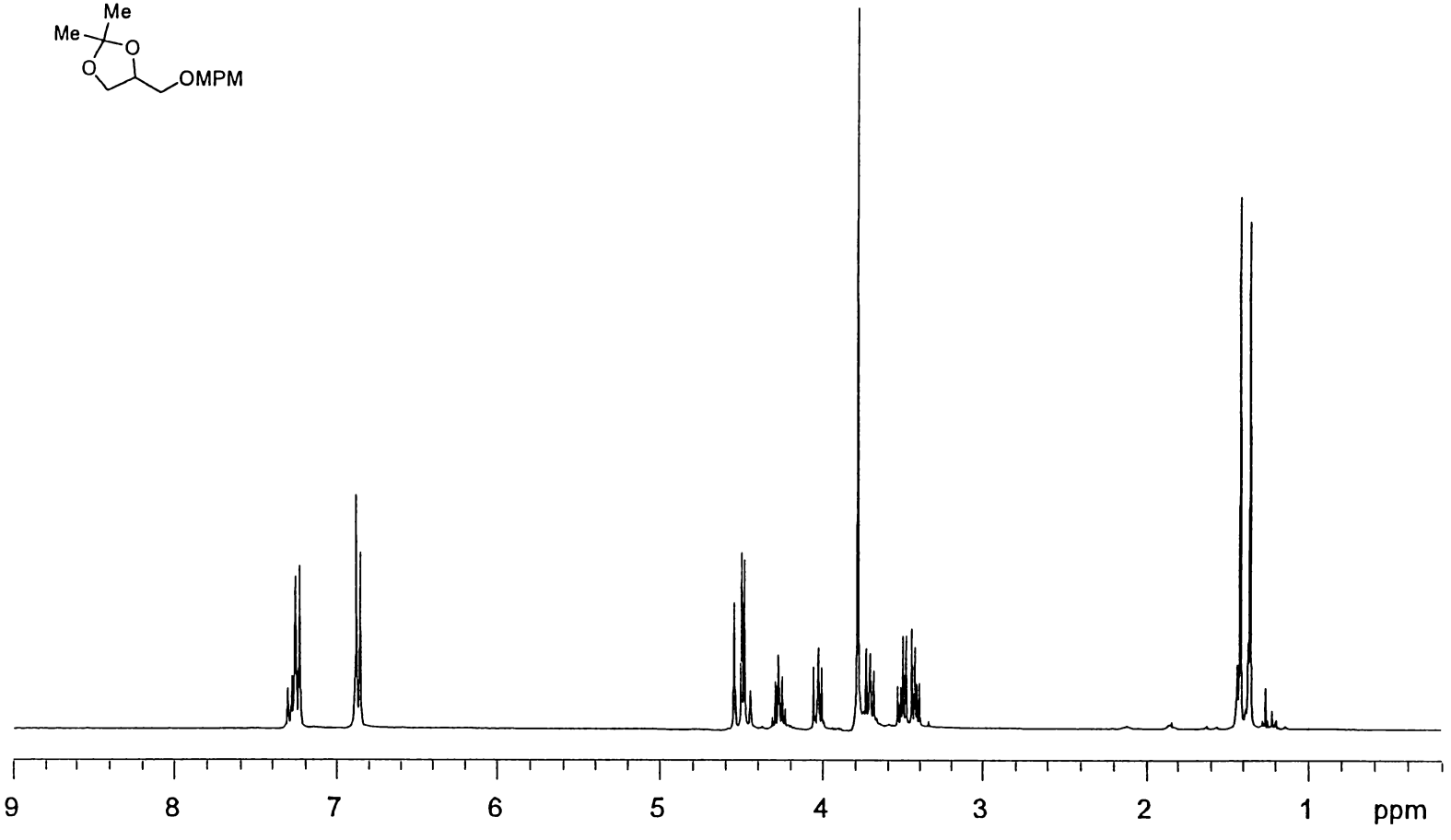
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
1-(*tert*-Butyldimethylsilyloxy)-2-(2-methoxy-ethoxymethoxymethyl)-but-3-en-2-ol (**56**).



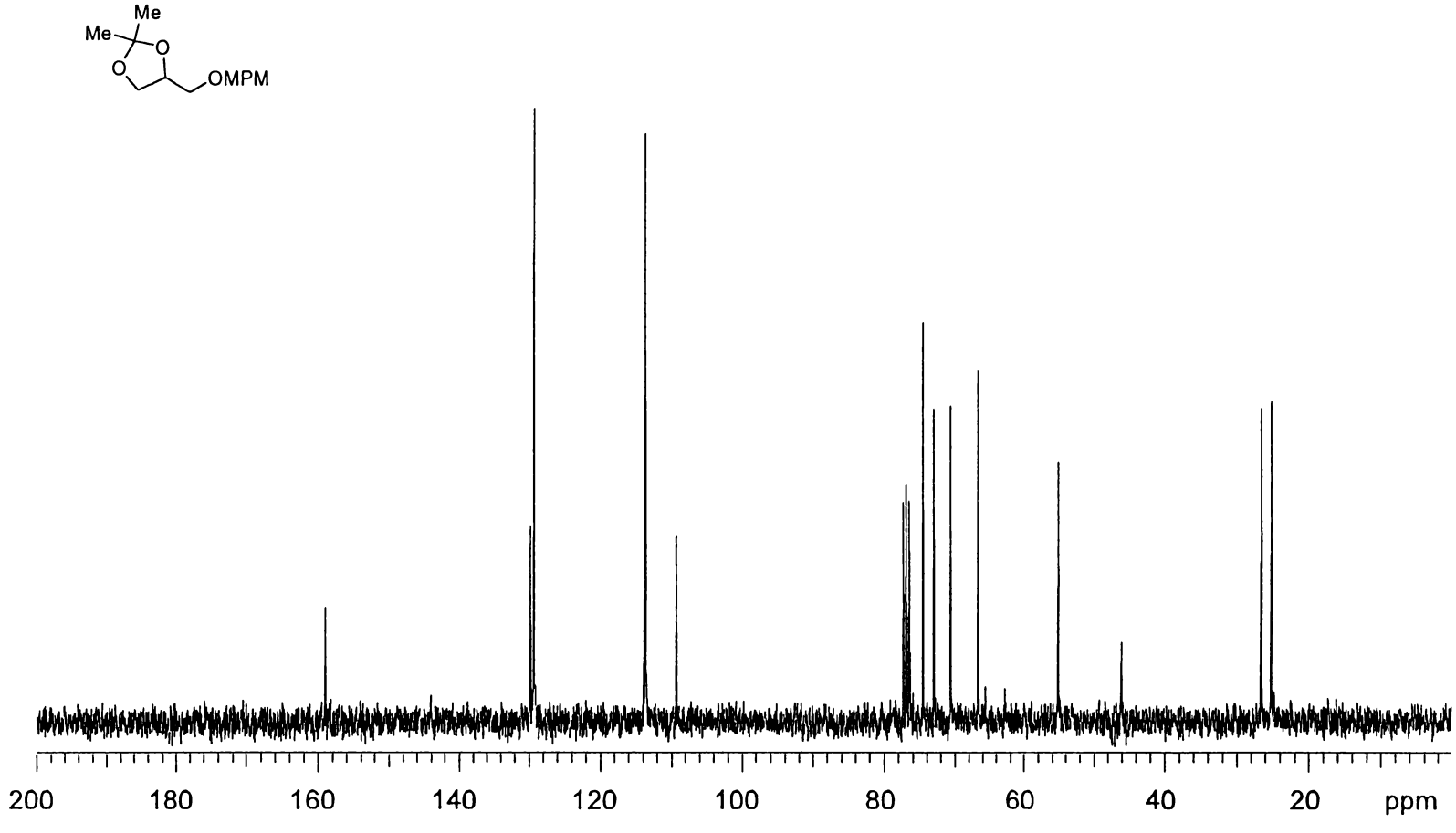
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
3,4-Bis-(*tert*-butyldimethylsilyloxy)-3-(2-methoxy-ethoxymethoxymethyl)-but-1-ene (**57**).



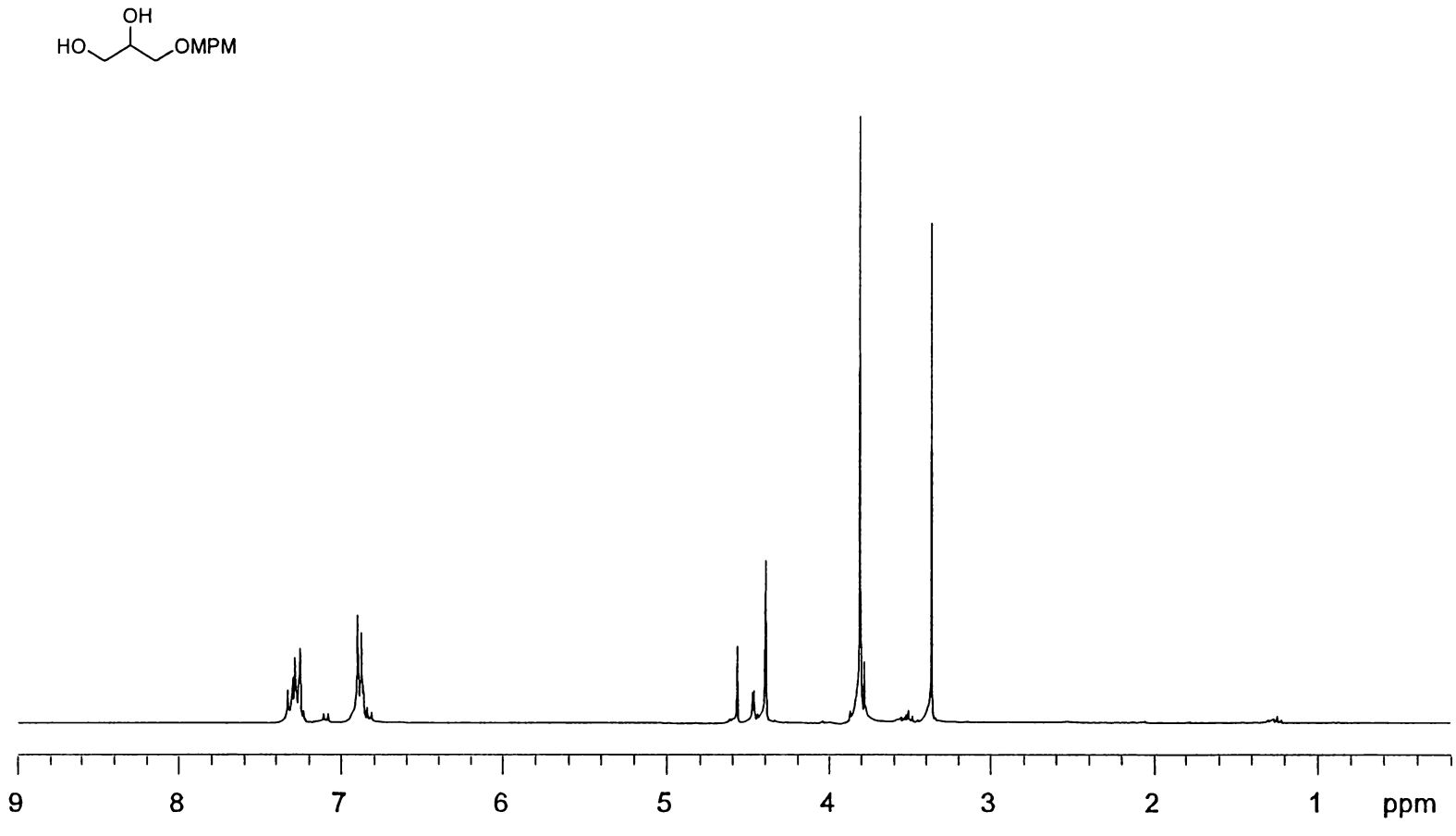
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of
3,4-Bis-(*tert*-butyldimethylsilyloxy)-3-(2-methoxy-ethoxymethoxymethyl)-but-1-ene (**57**).



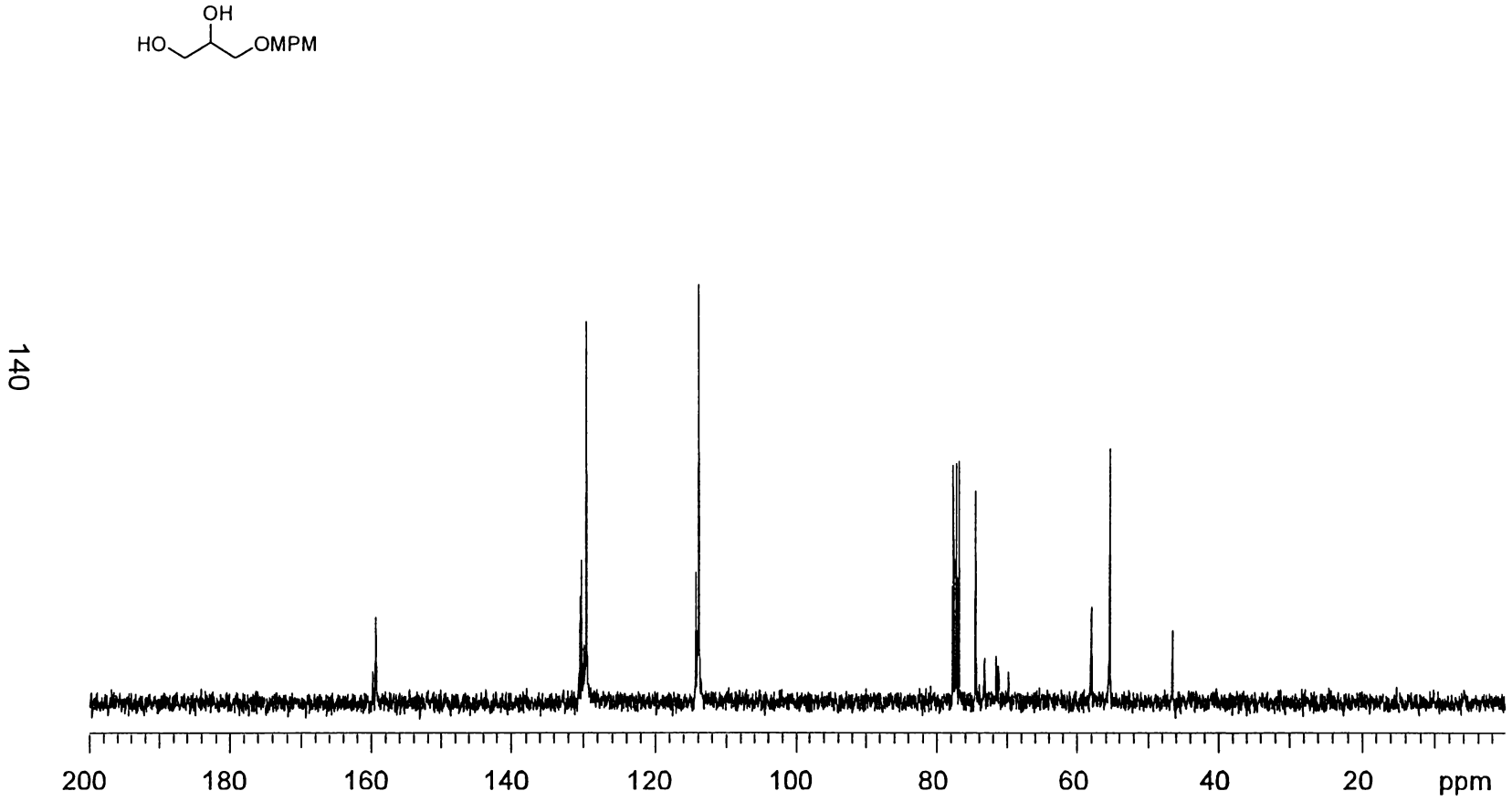
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 4-(4-Methoxy-benzyloxymethyl)-2,2-dimethyl-[1,3]dioxolane (**59**).



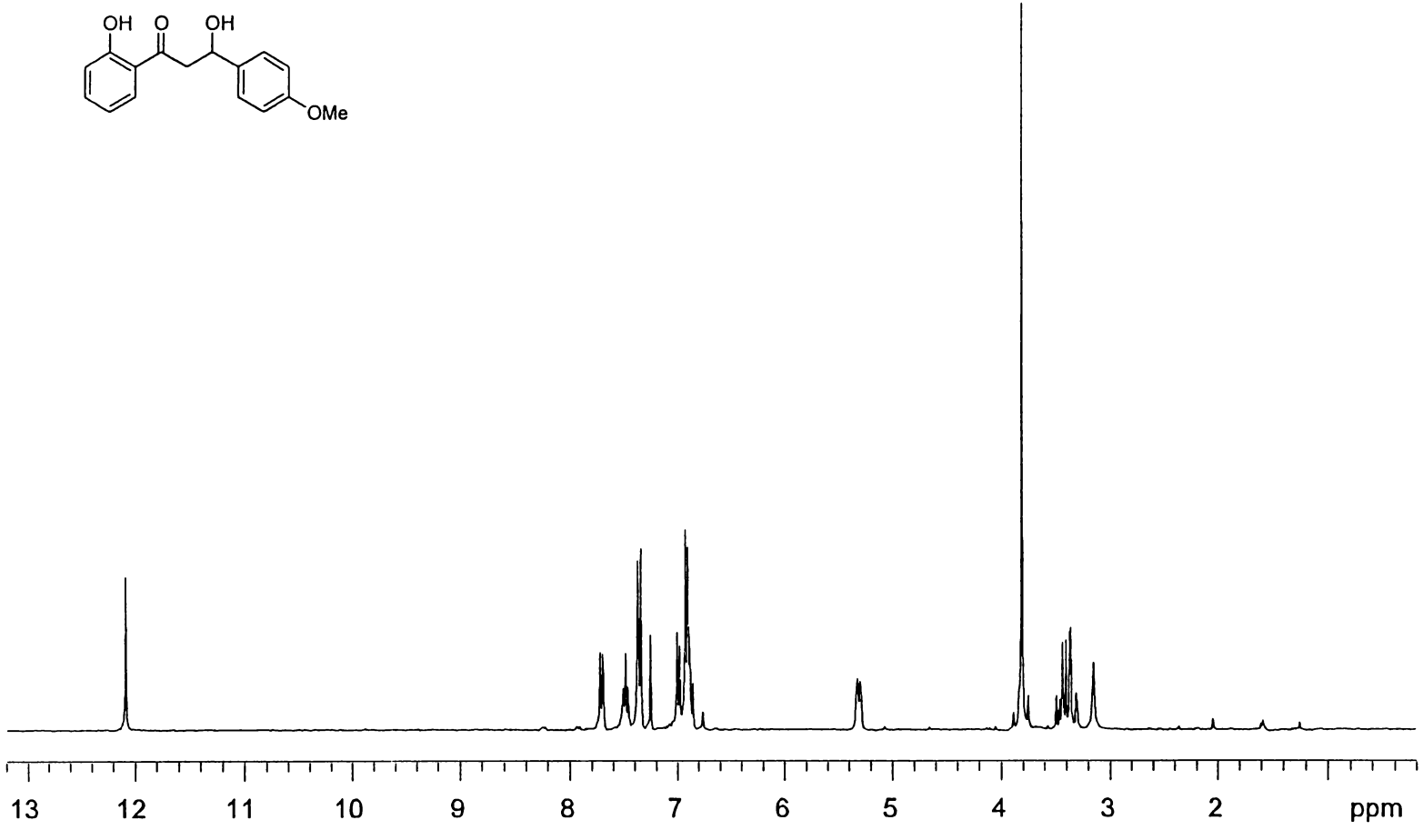
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 4-(4-Methoxy-benzyloxymethyl)-2,2-dimethyl-[1,3]dioxolane (**59**).



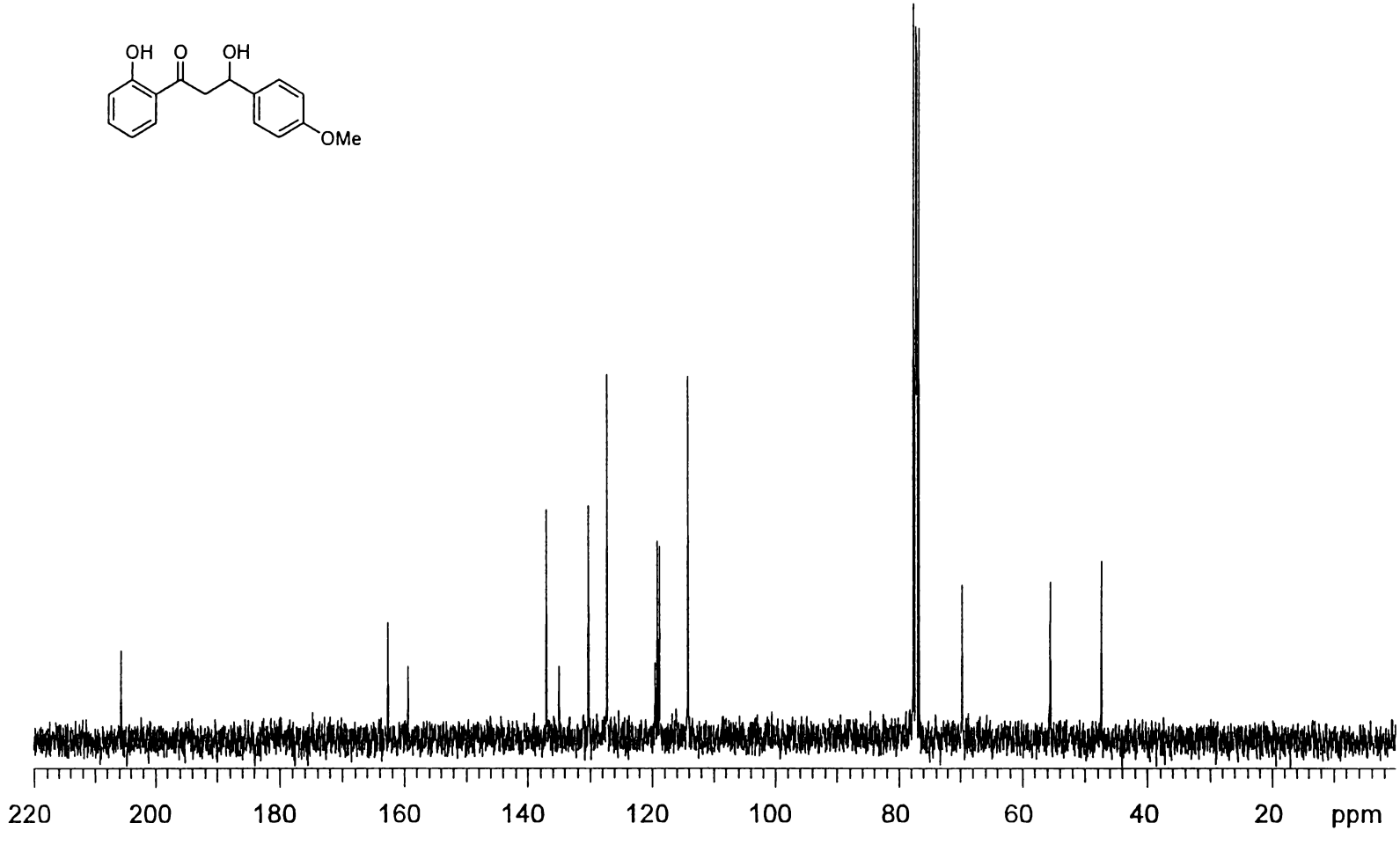
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 3-(4-Methoxy-benzyloxy)-propane-1,2-diol (**60**).



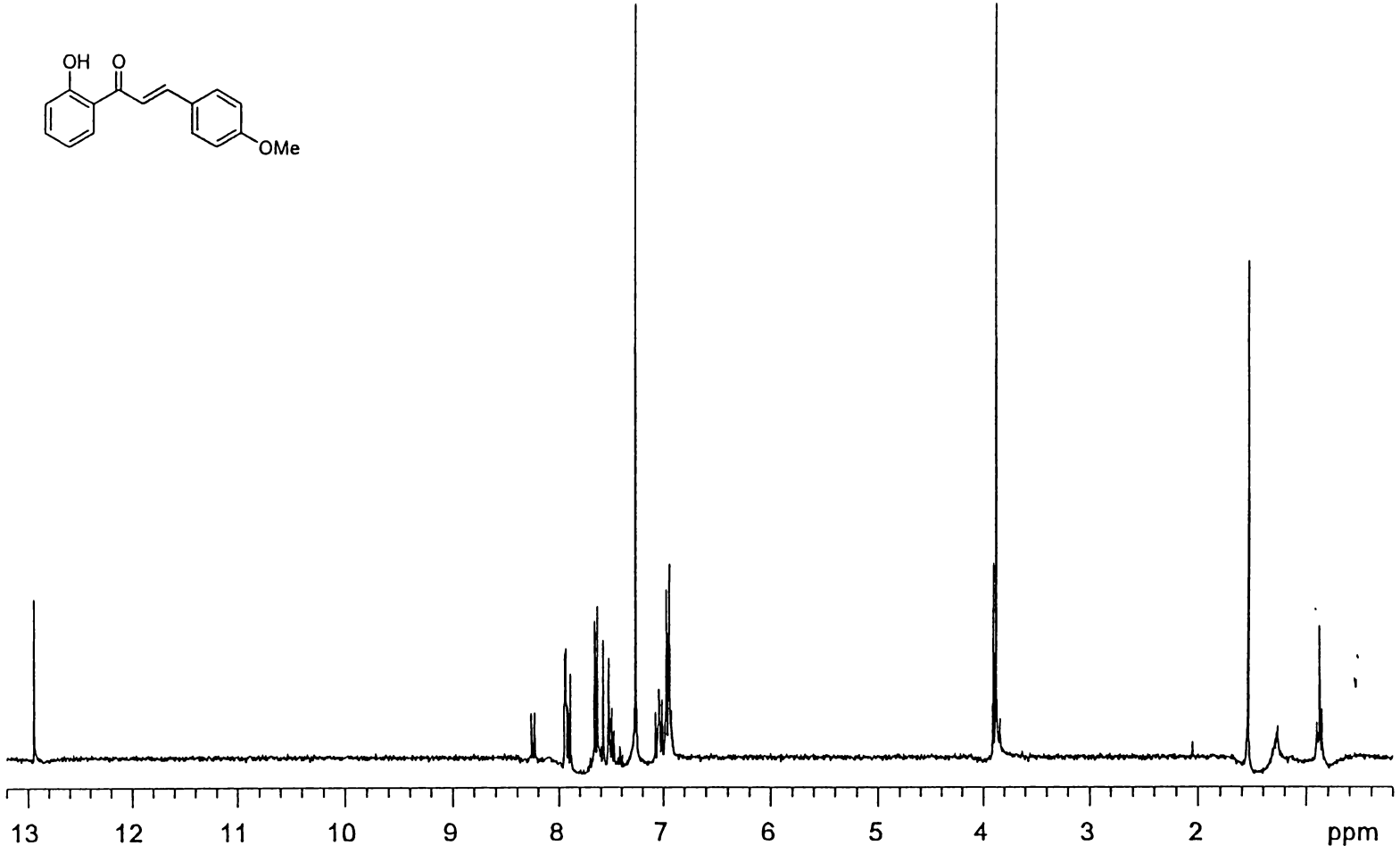
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 3-(4-Methoxy-benzyloxy)-propane-1,2-diol (**60**).



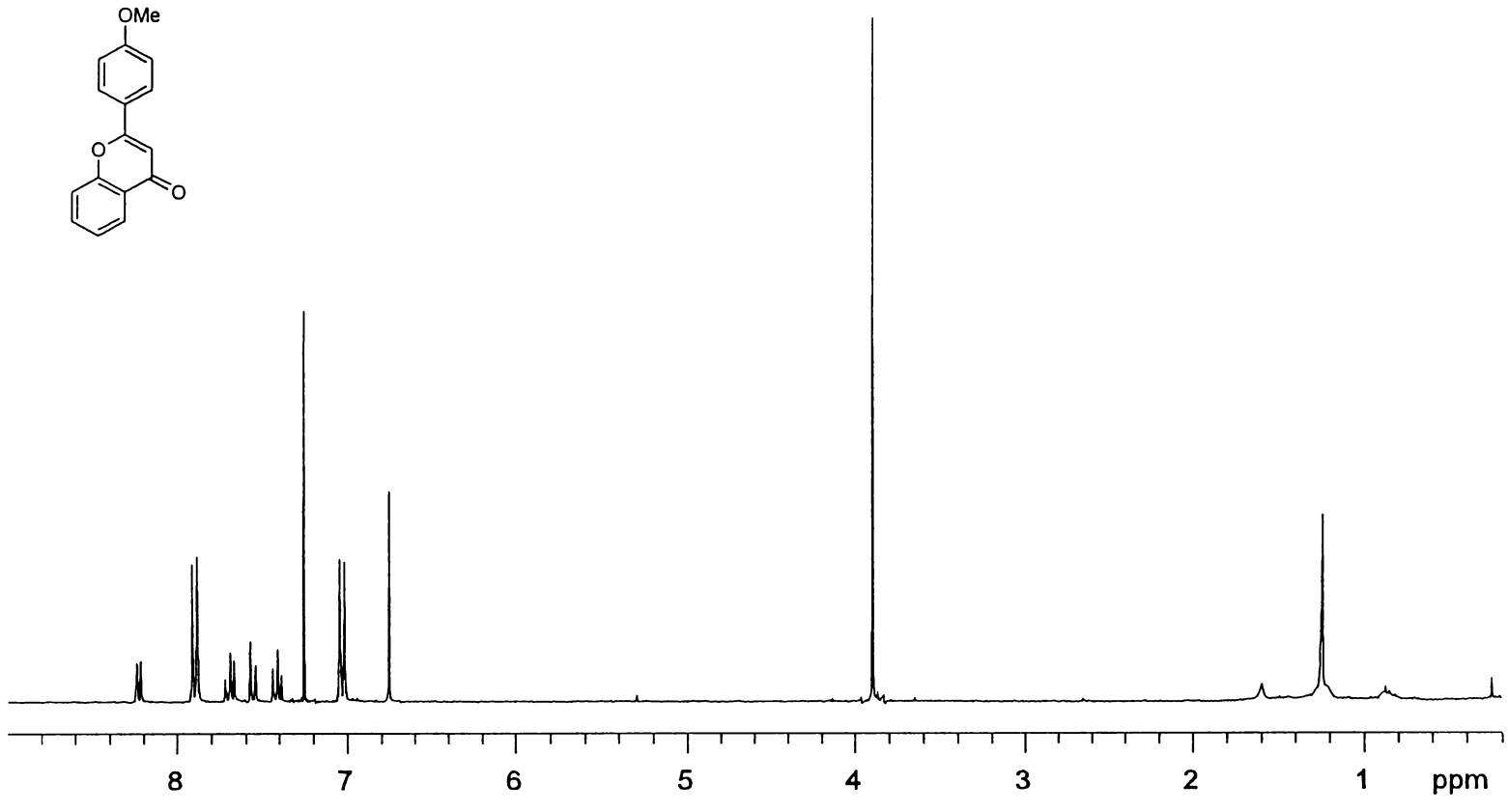
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 3-Hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-propan-1-one (**71**).



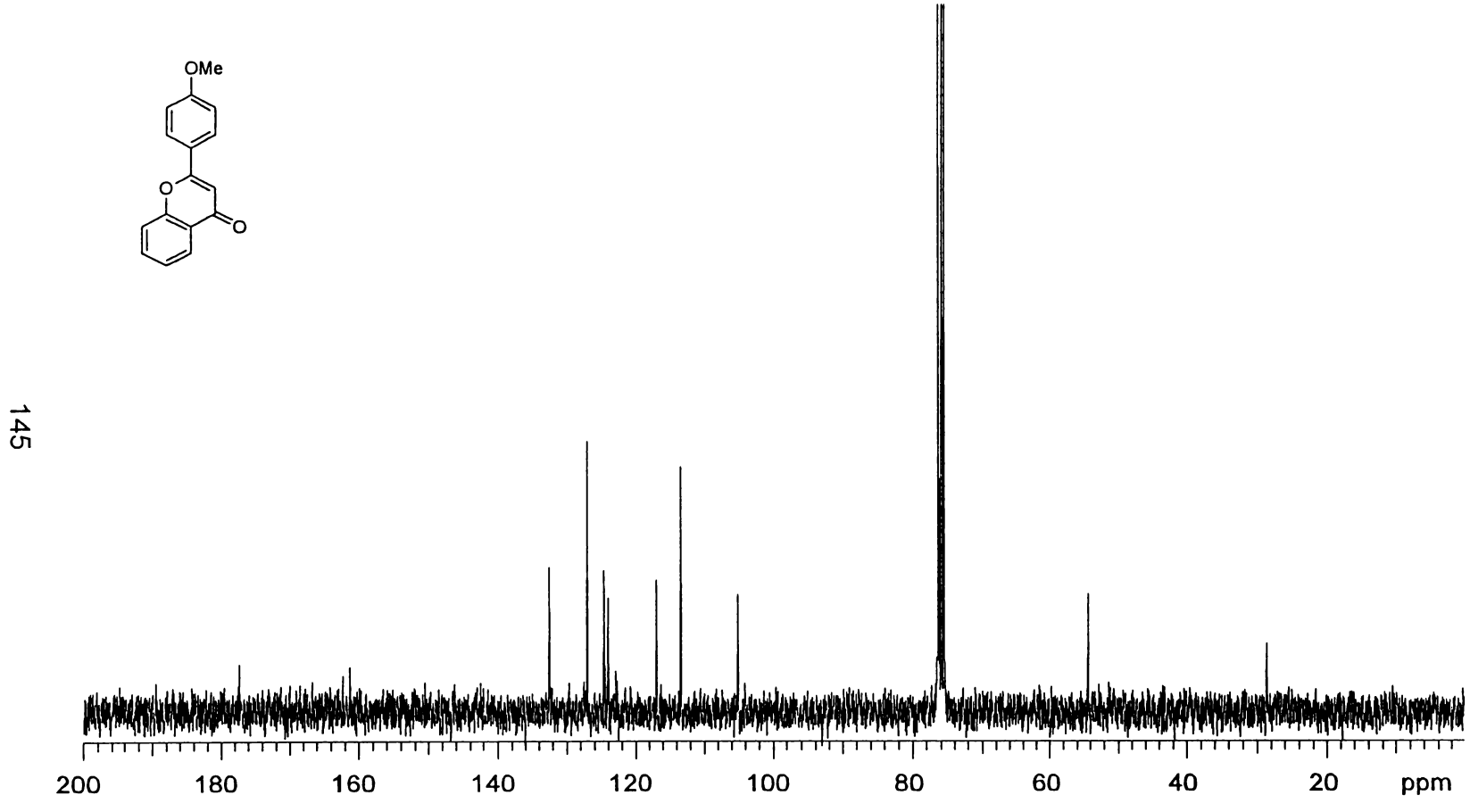
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 3-Hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-propan-1-one (**71**).



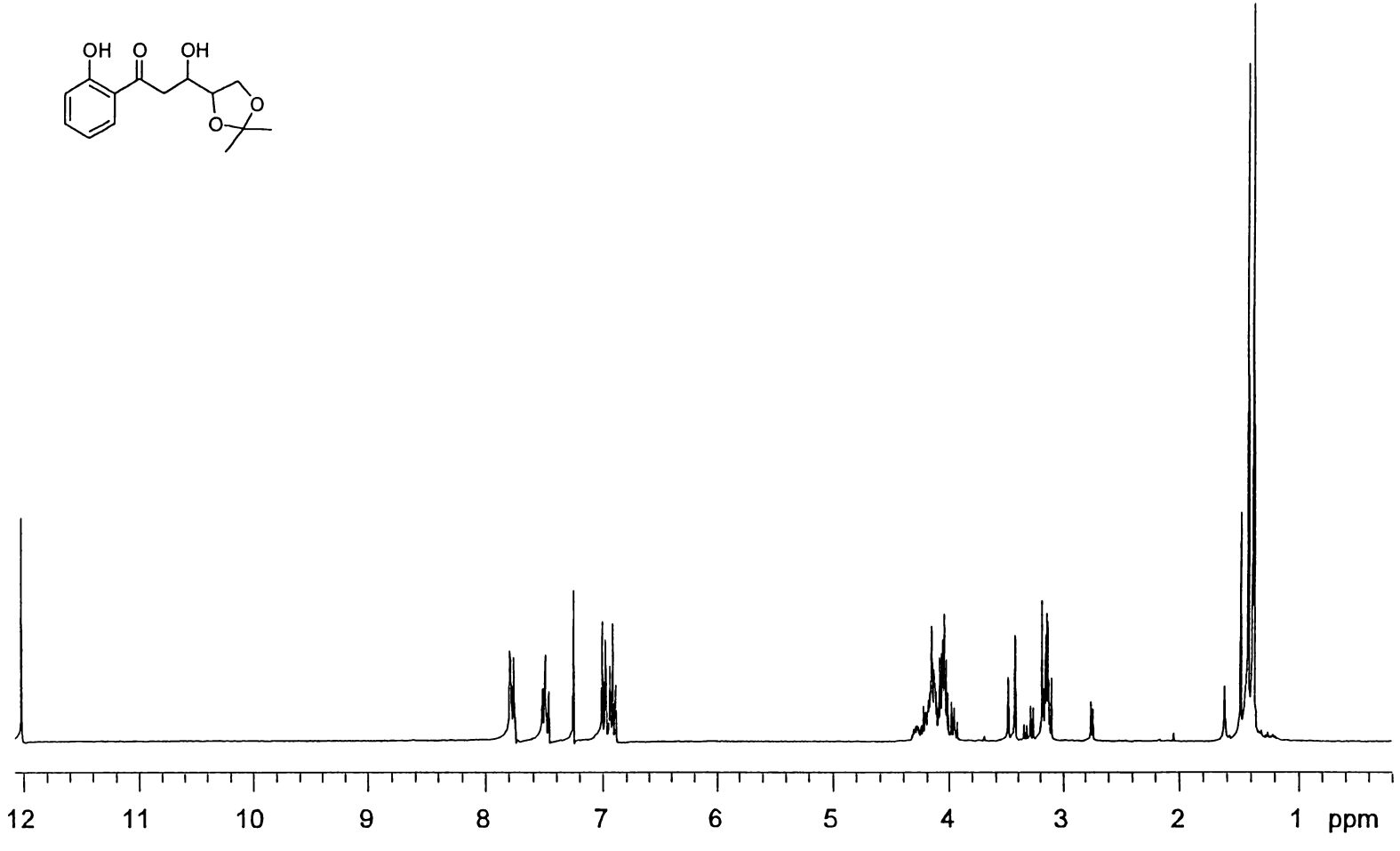
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-propanone (**72**).



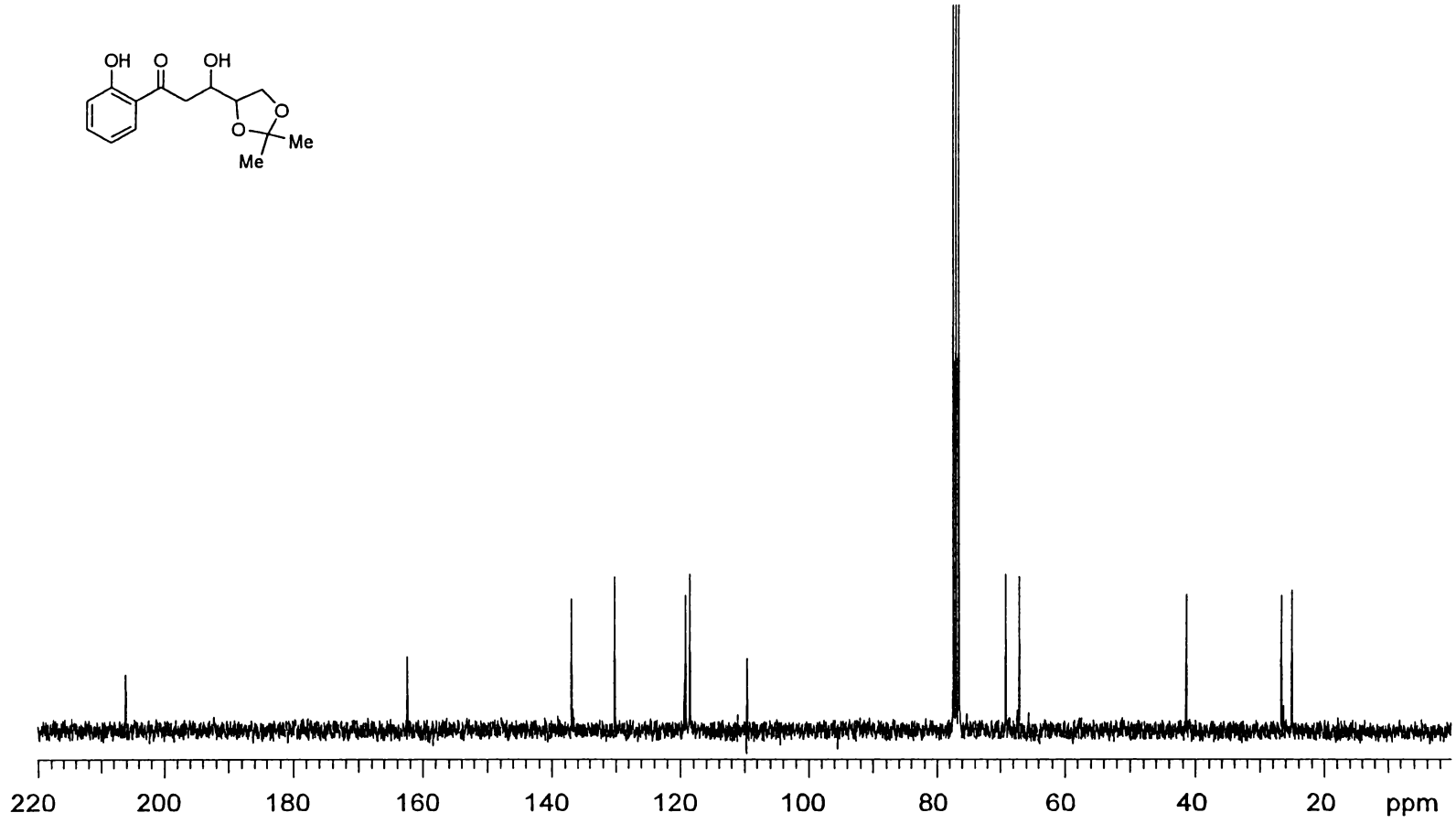
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-(4-Methoxyphenyl)chromen-4-one (**73**).



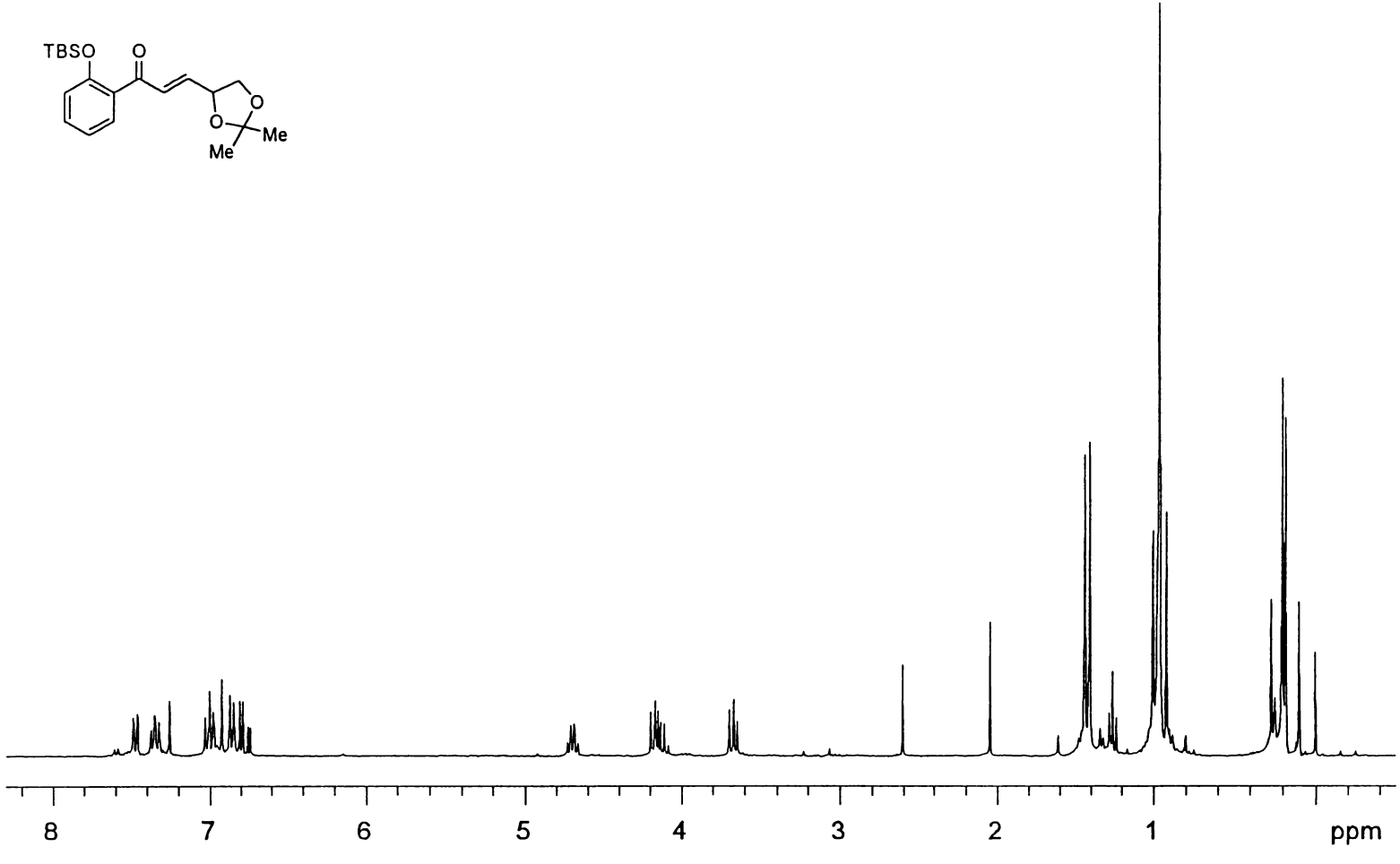
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-(4-Methoxyphenyl)chromen-4-one (**73**).



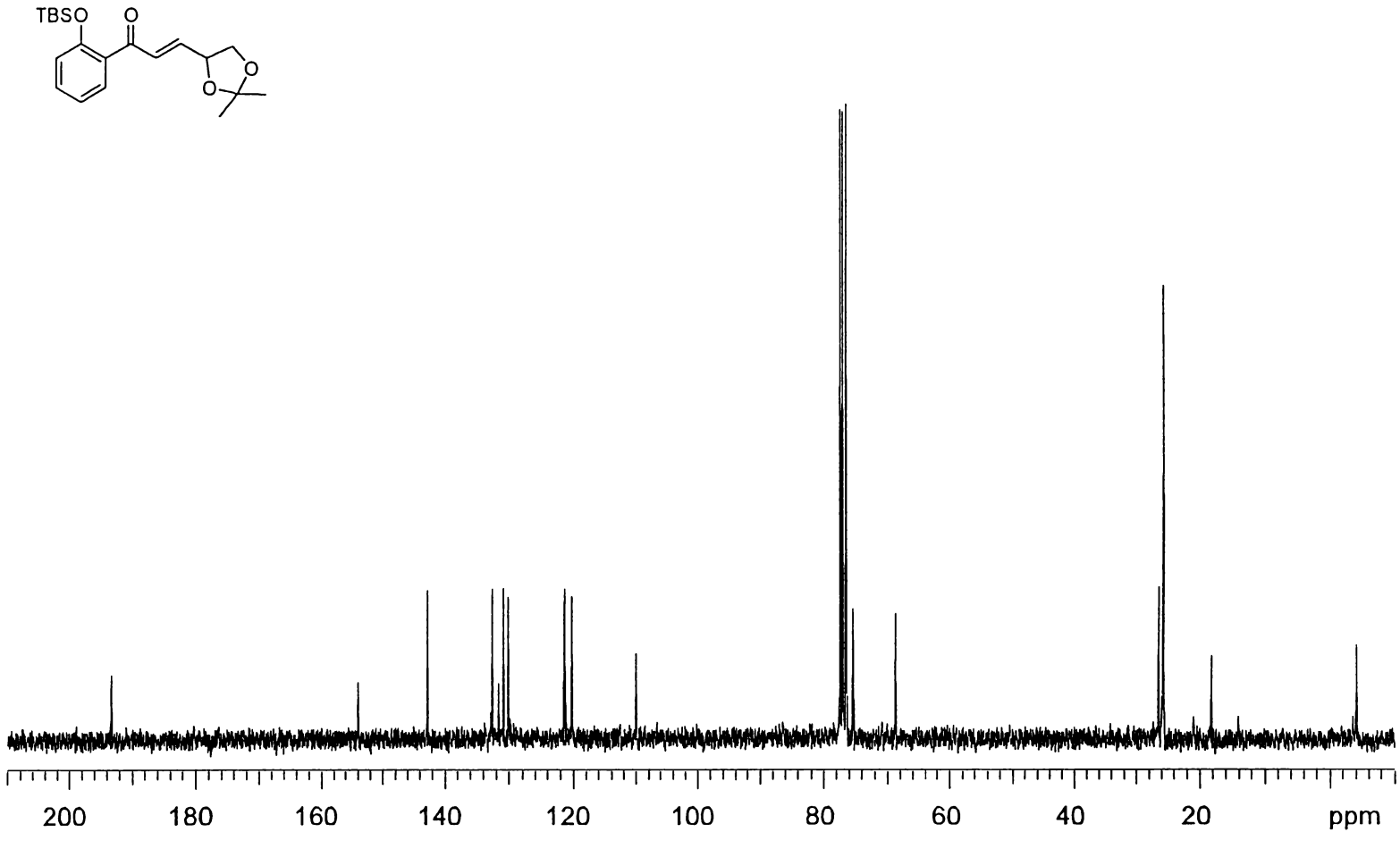
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-hydroxy-1-(2-hydroxyphenyl)-propan-1-one (**74**).



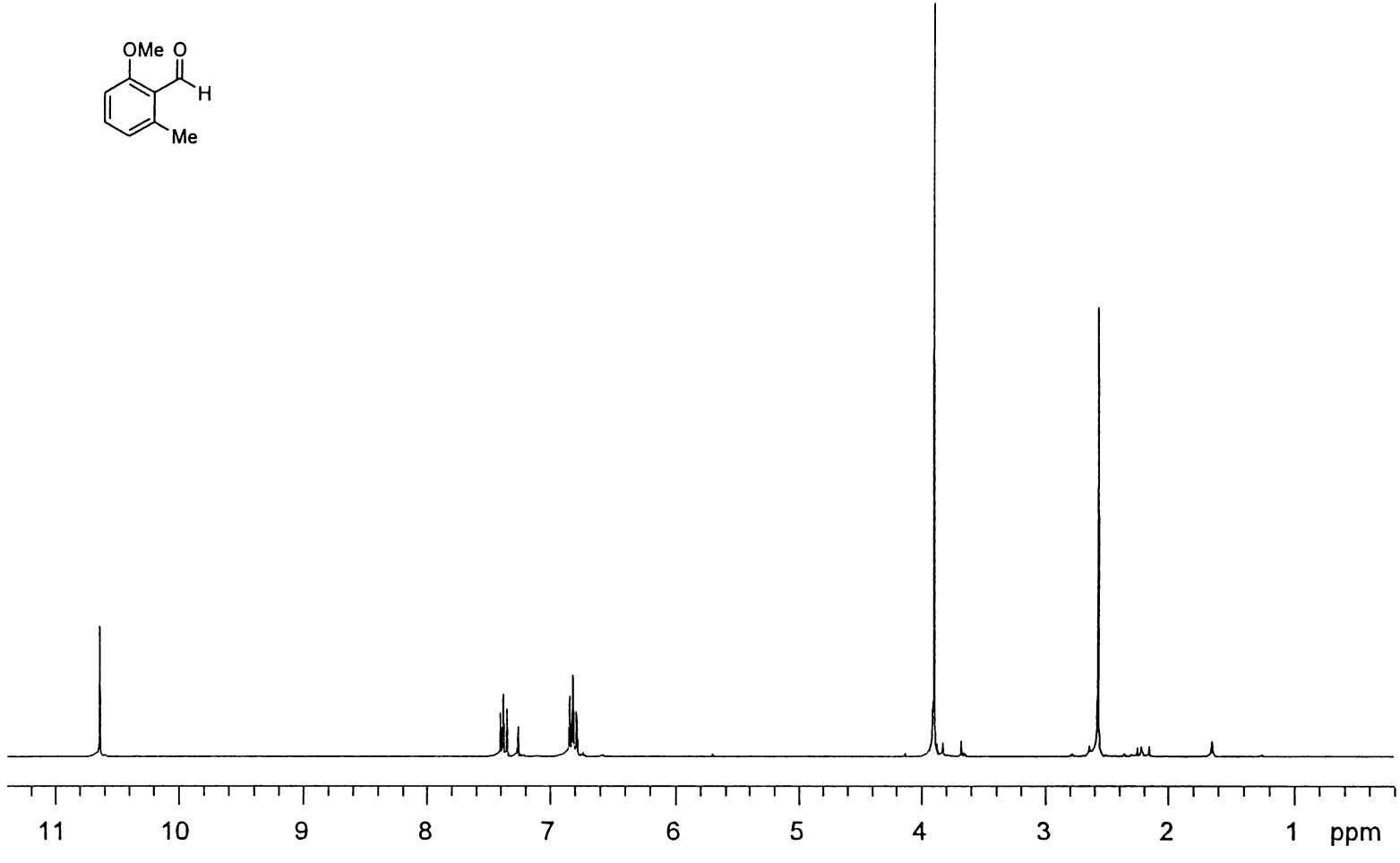
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of
3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-hydroxy-1-(2-hydroxyphenyl)propan-1-one (**74**).



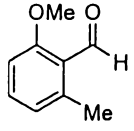
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
1-[2-(*tert*-Butyldimethylsilyloxy)-phenyl]-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-propenone (**76**).

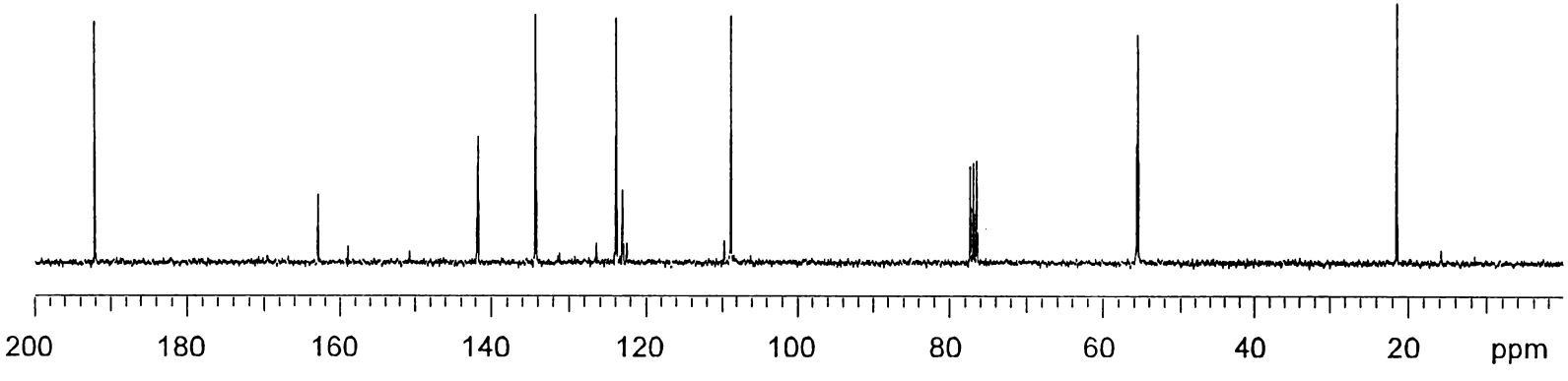


^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of
1-[2-(*tert*-Butyldimethylsilyloxy-phenyl)]-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-propenone (**76**).

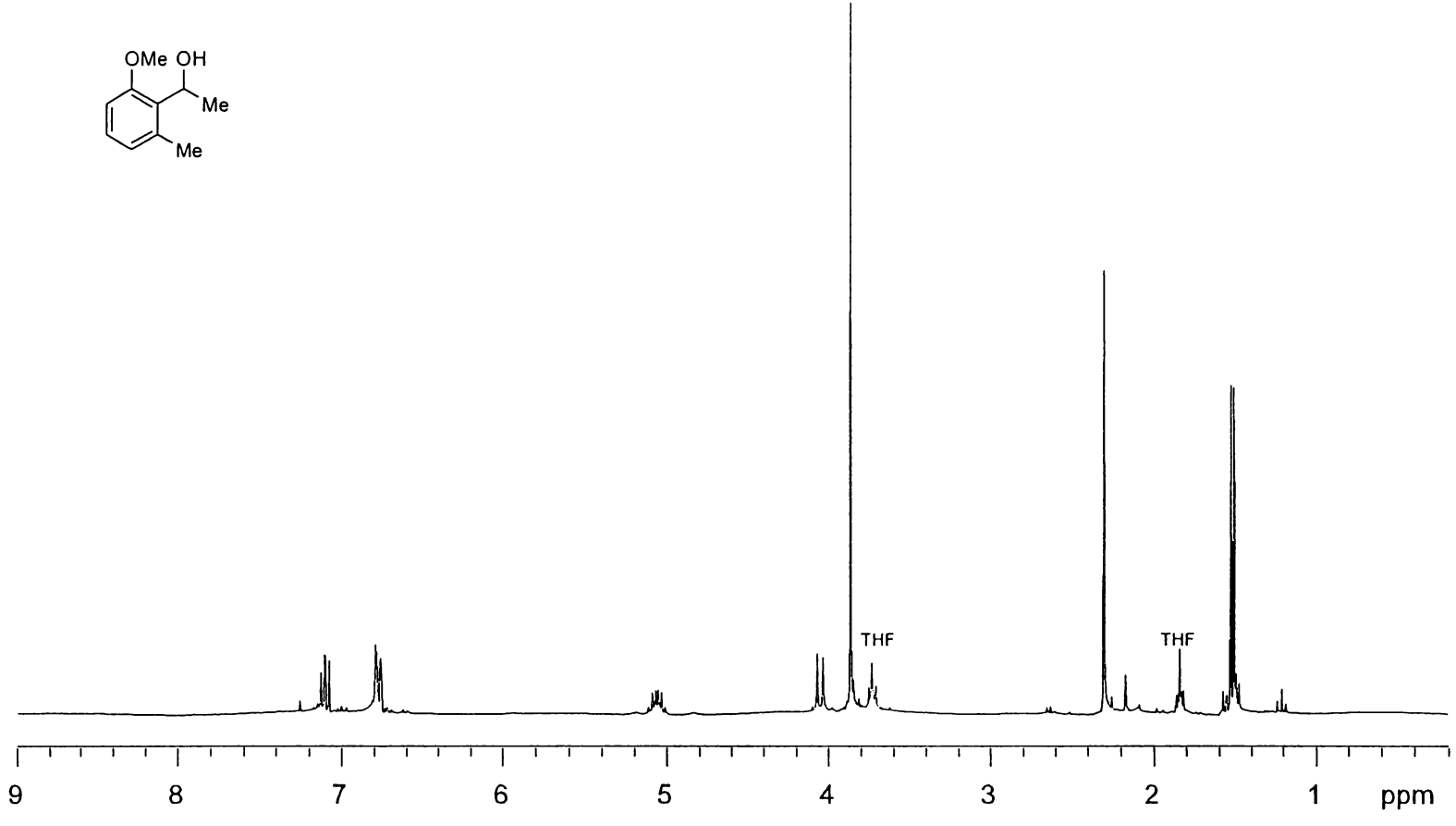


^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Methoxy-6-methylbenzaldehyde (**38**).

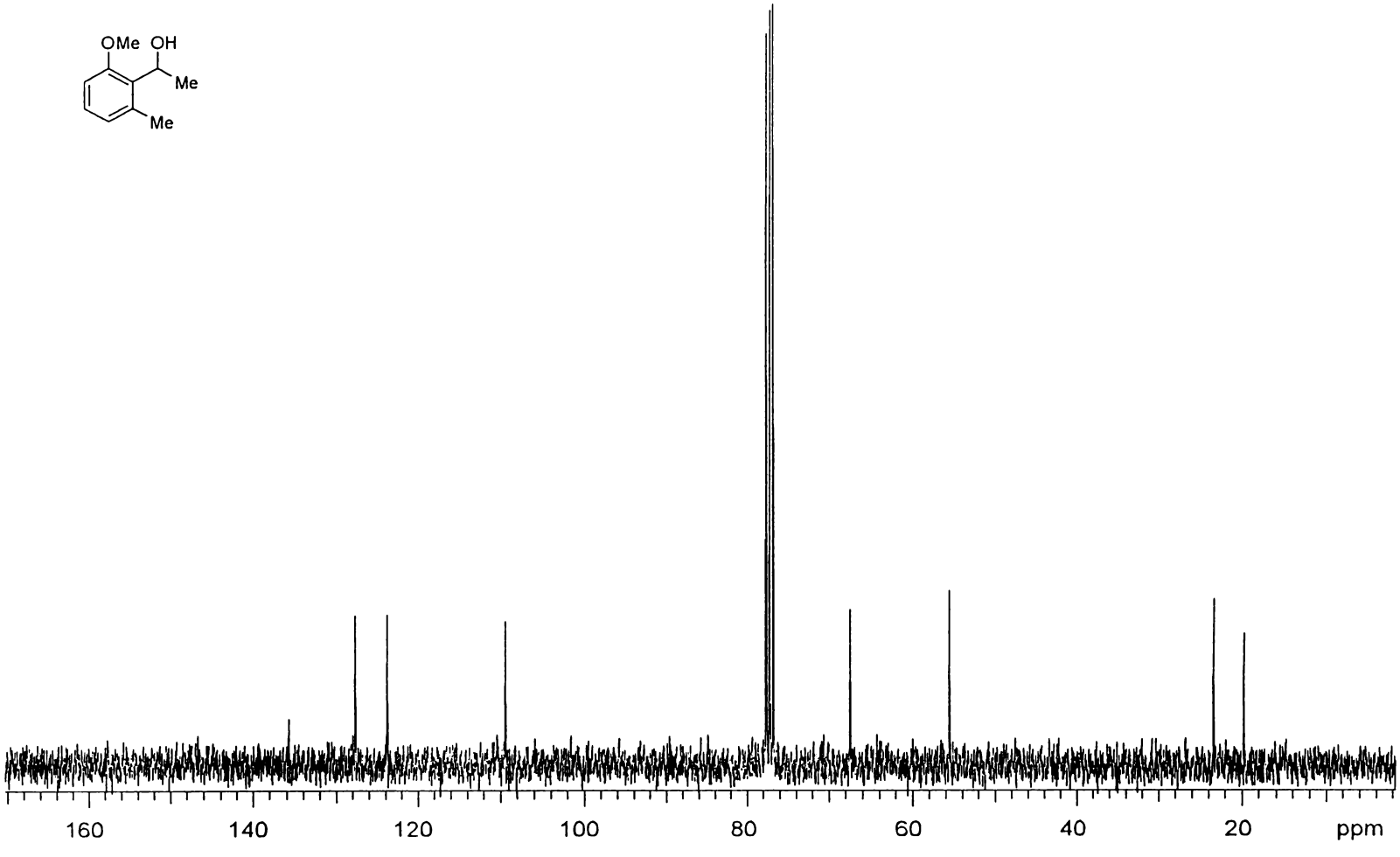




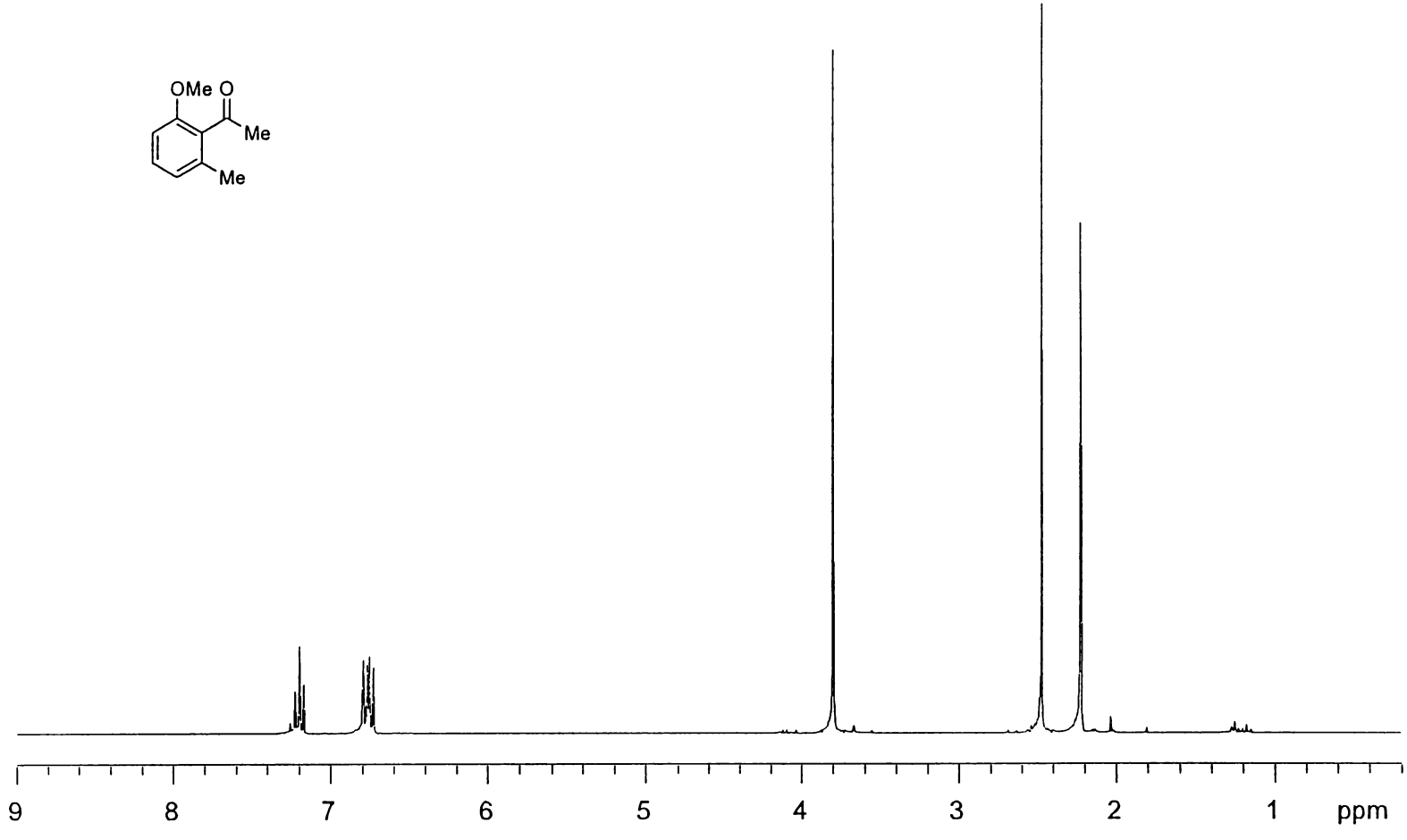
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Methoxy-6-methylbenzaldehyde (**38**).



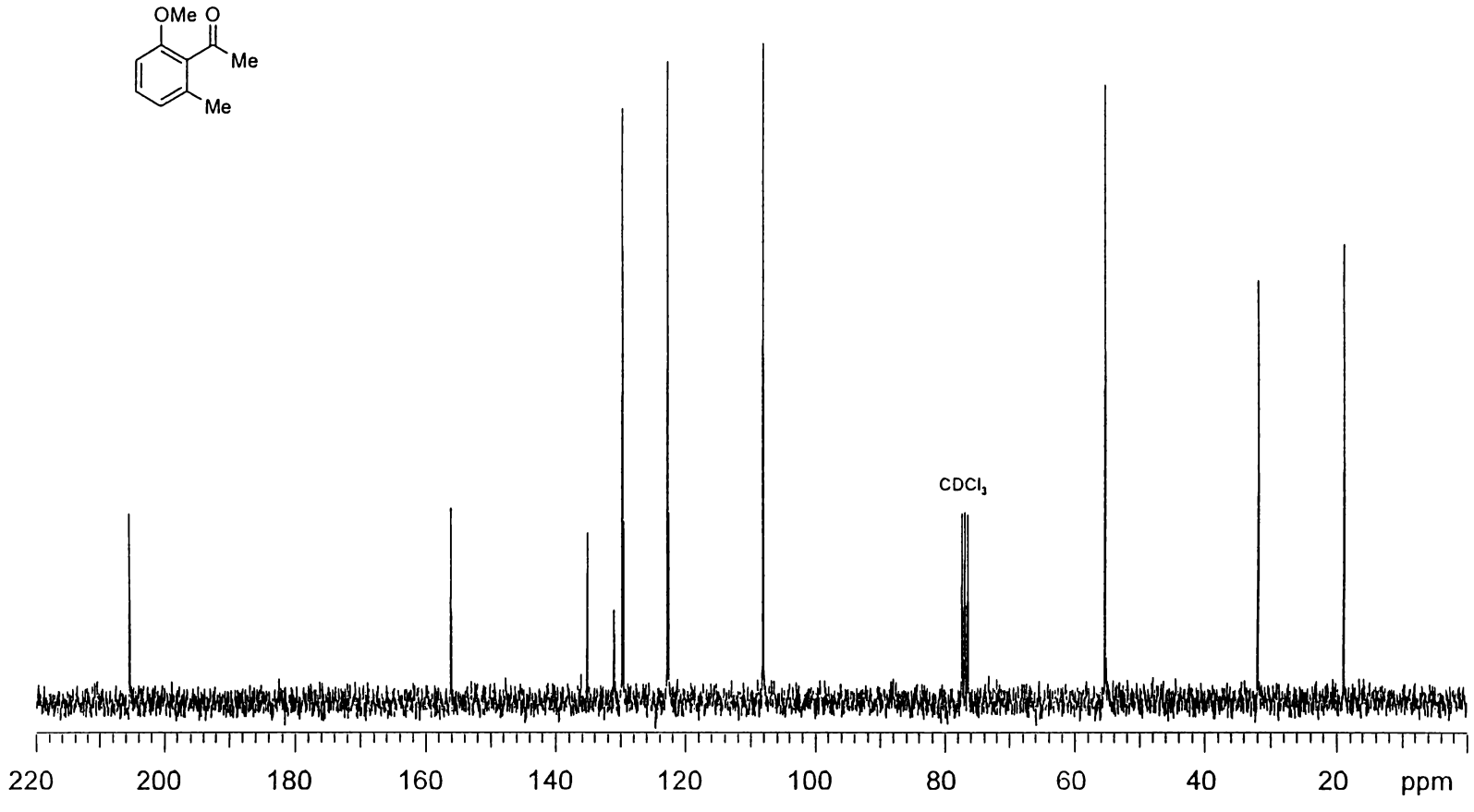
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-(2-Methoxy-6-methylphenyl)ethanol (**39**).



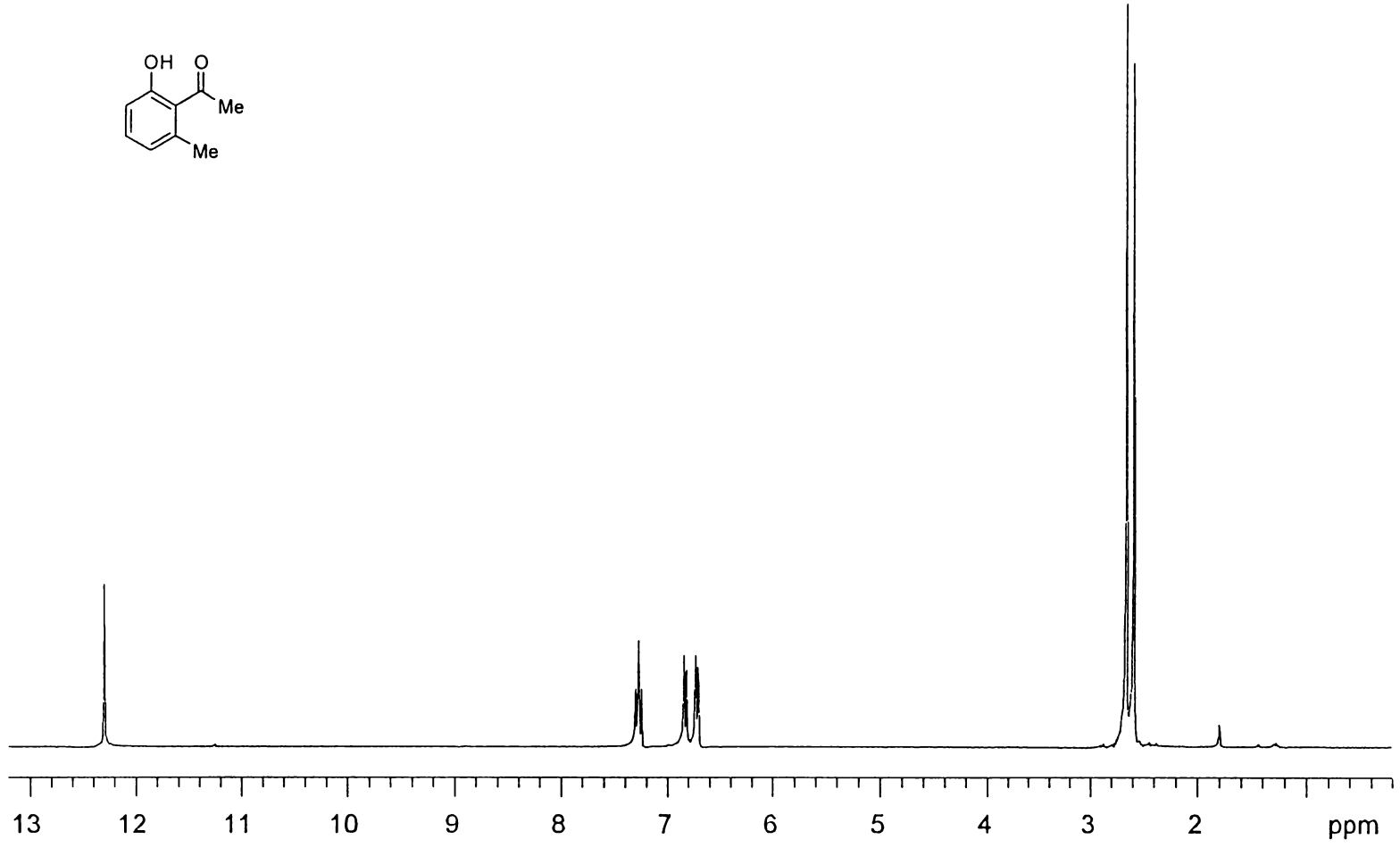
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 1-(2-Methoxy-6-methylphenyl)ethanol (**39**).



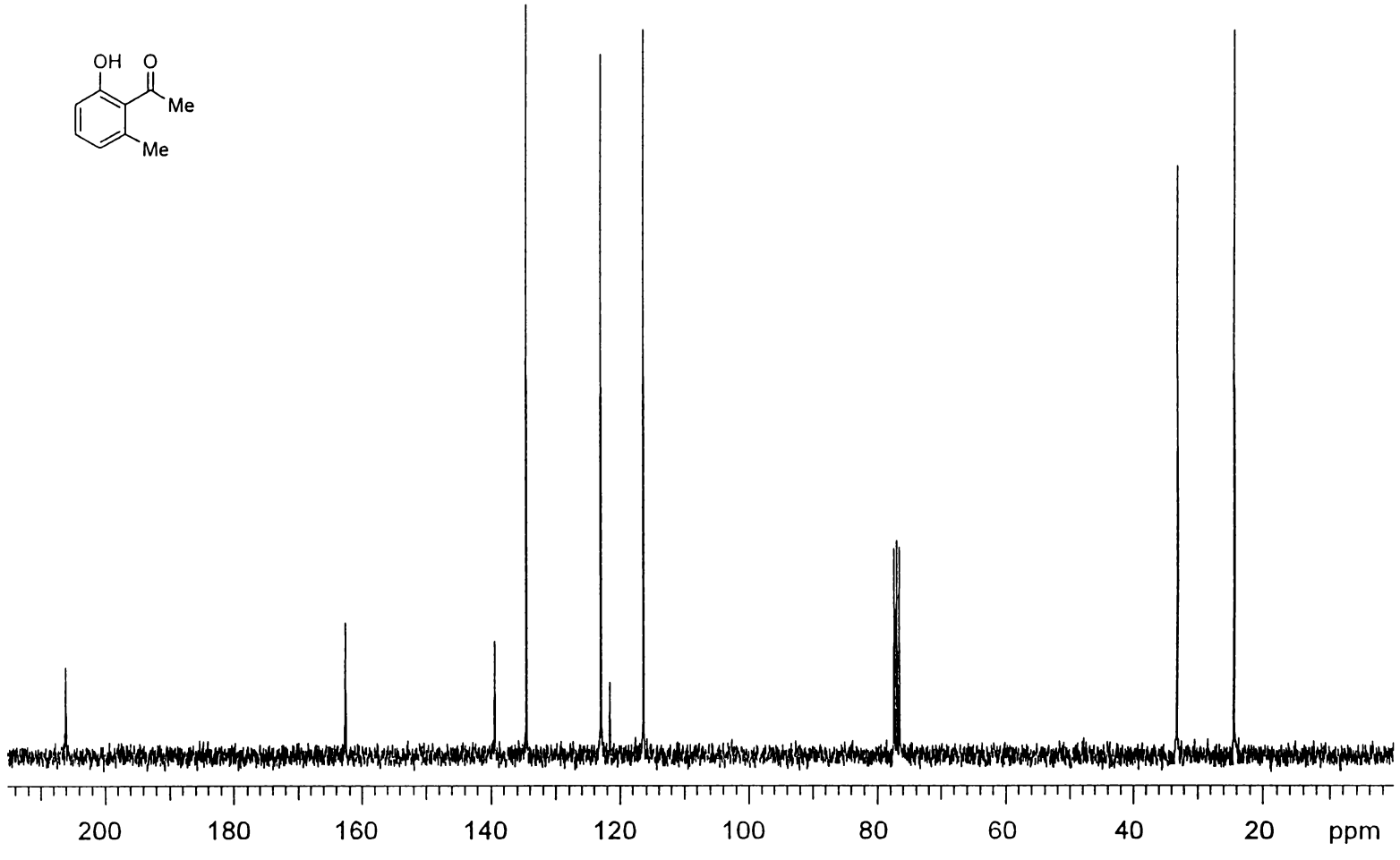
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Methoxy-6-methylacetophenone (**40**).



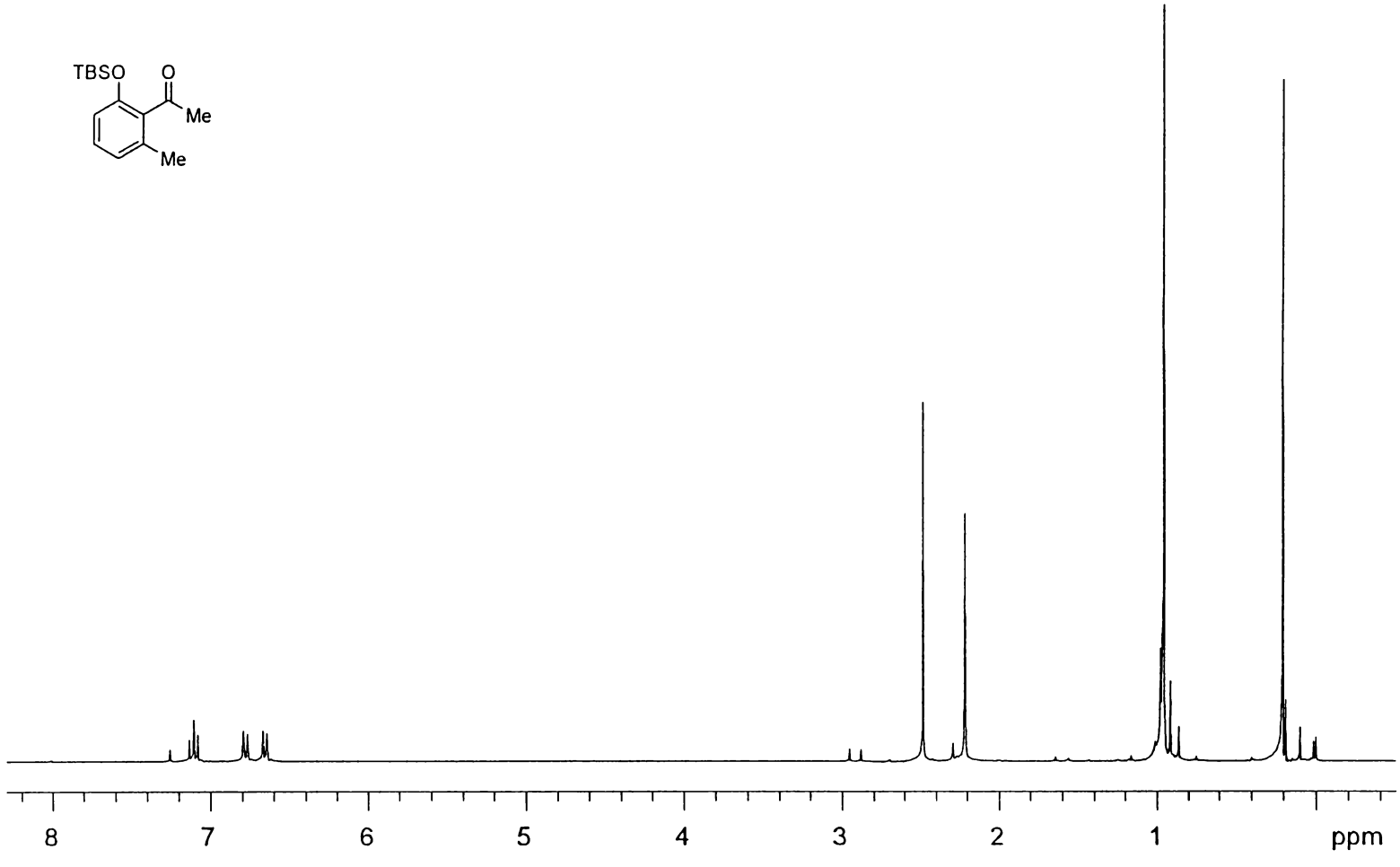
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Methoxy-6-methylacetophenone (**40**).



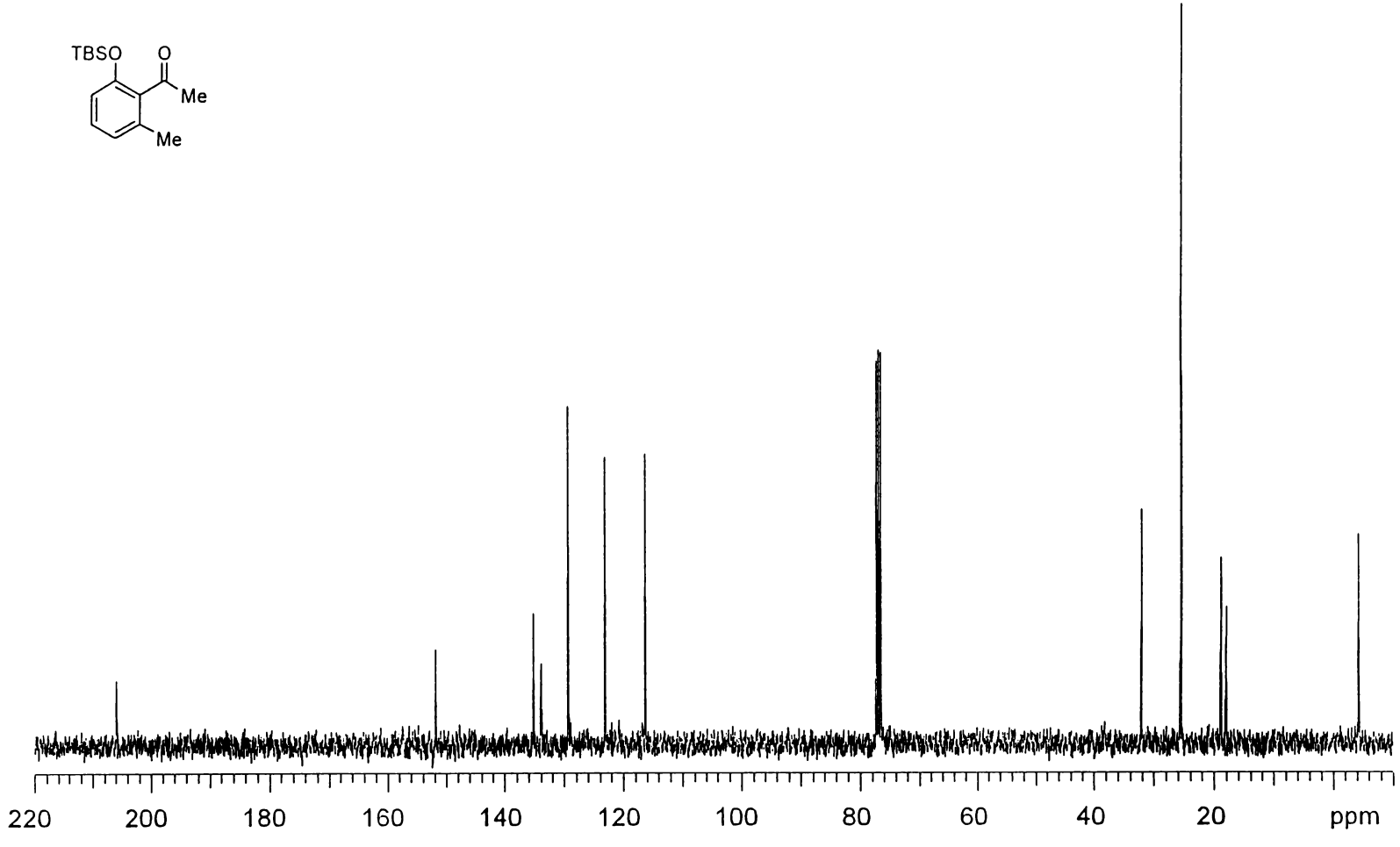
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Hydroxy-6-methylacetophenone (**69**).



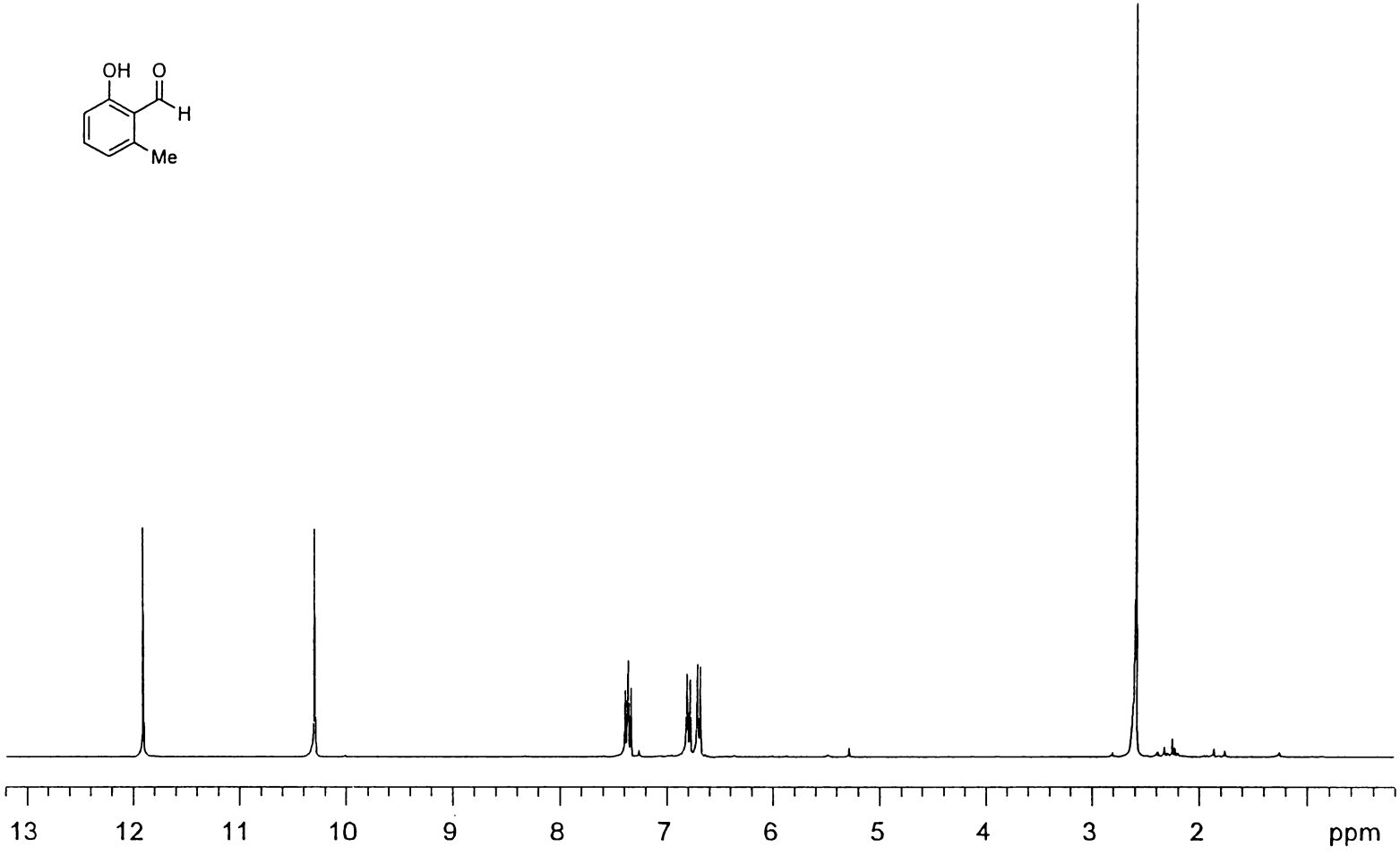
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Hydroxy-6-methylacetophenone (**69**).



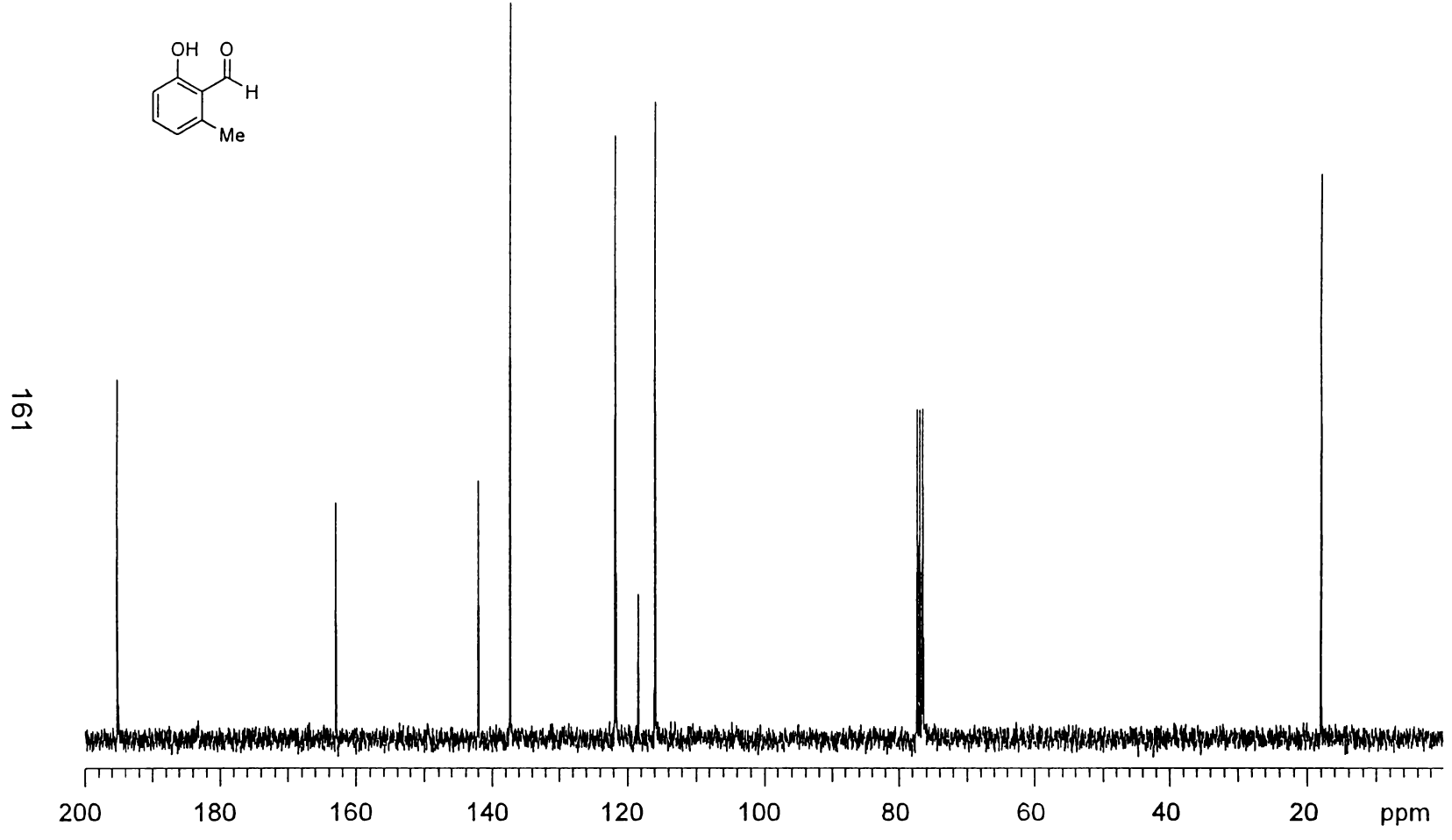
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-(*tert*-Butyldimethylsilyloxy)-6-methylacetophenone (**70**).



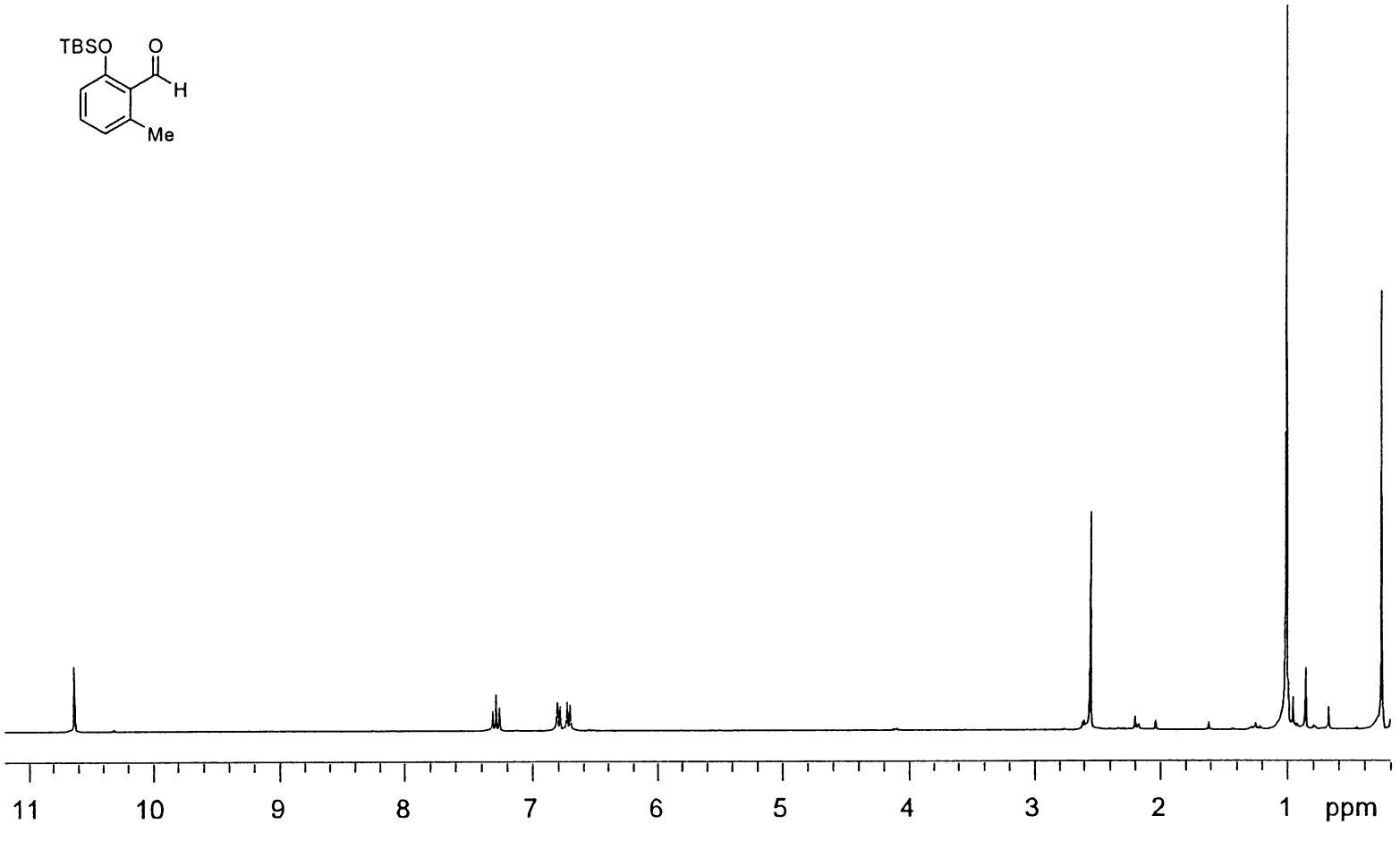
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-(*tert*-Butyldimethylsilyloxy)-6-methylacetophenone (**70**).



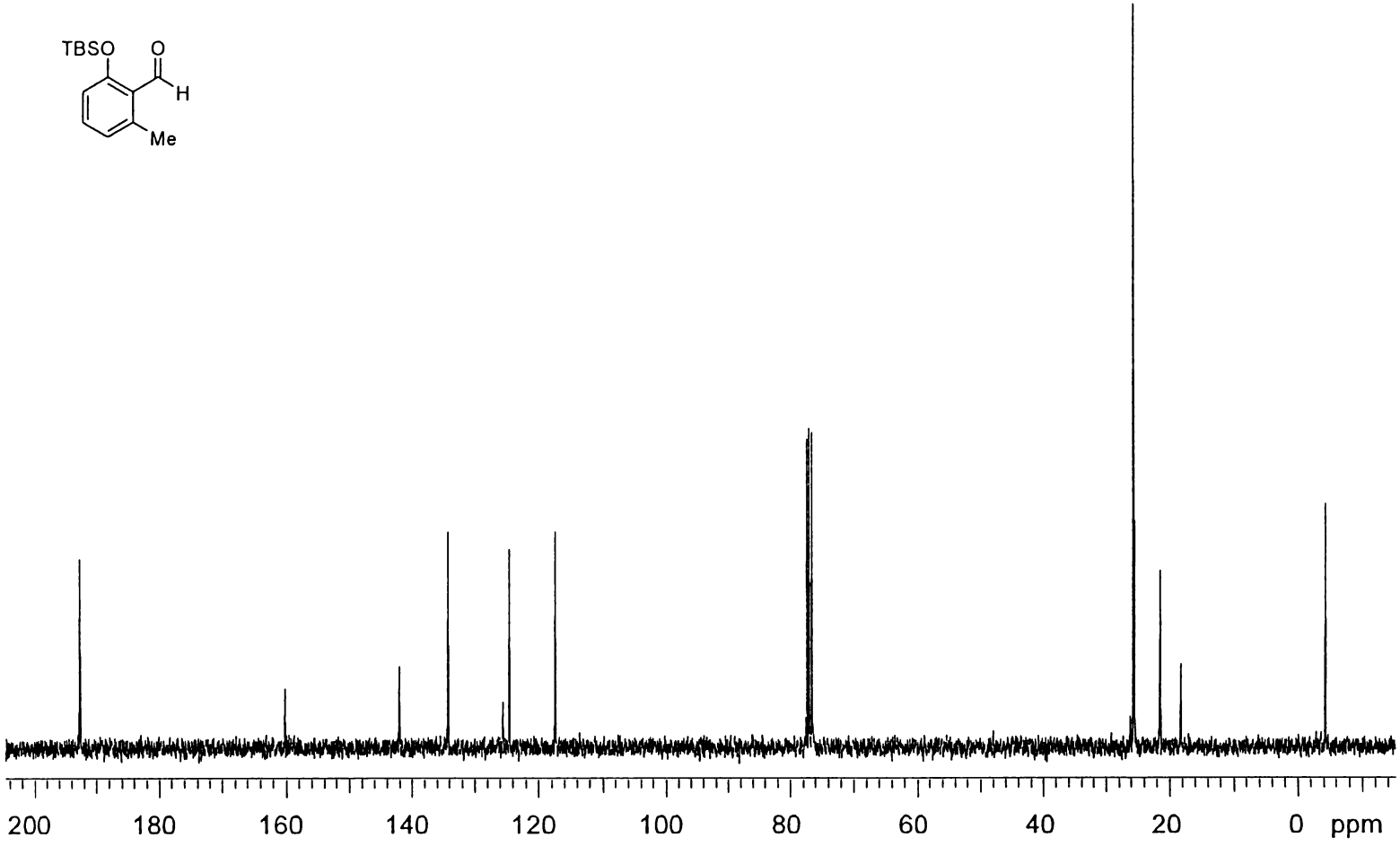
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 6-Methylsalicylaldehyde (**80**).



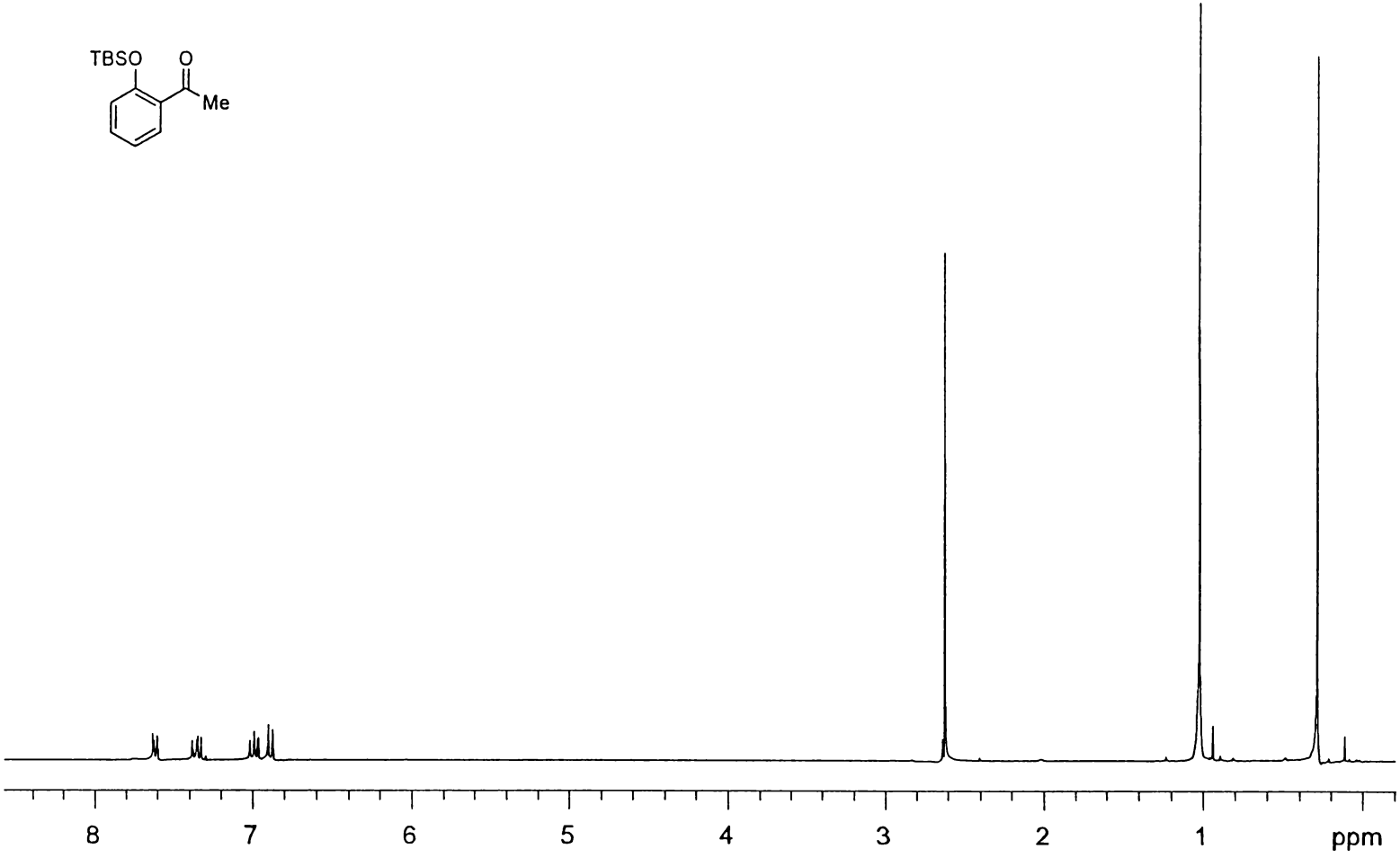
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 6-Methylsalicylaldehyde (**80**).



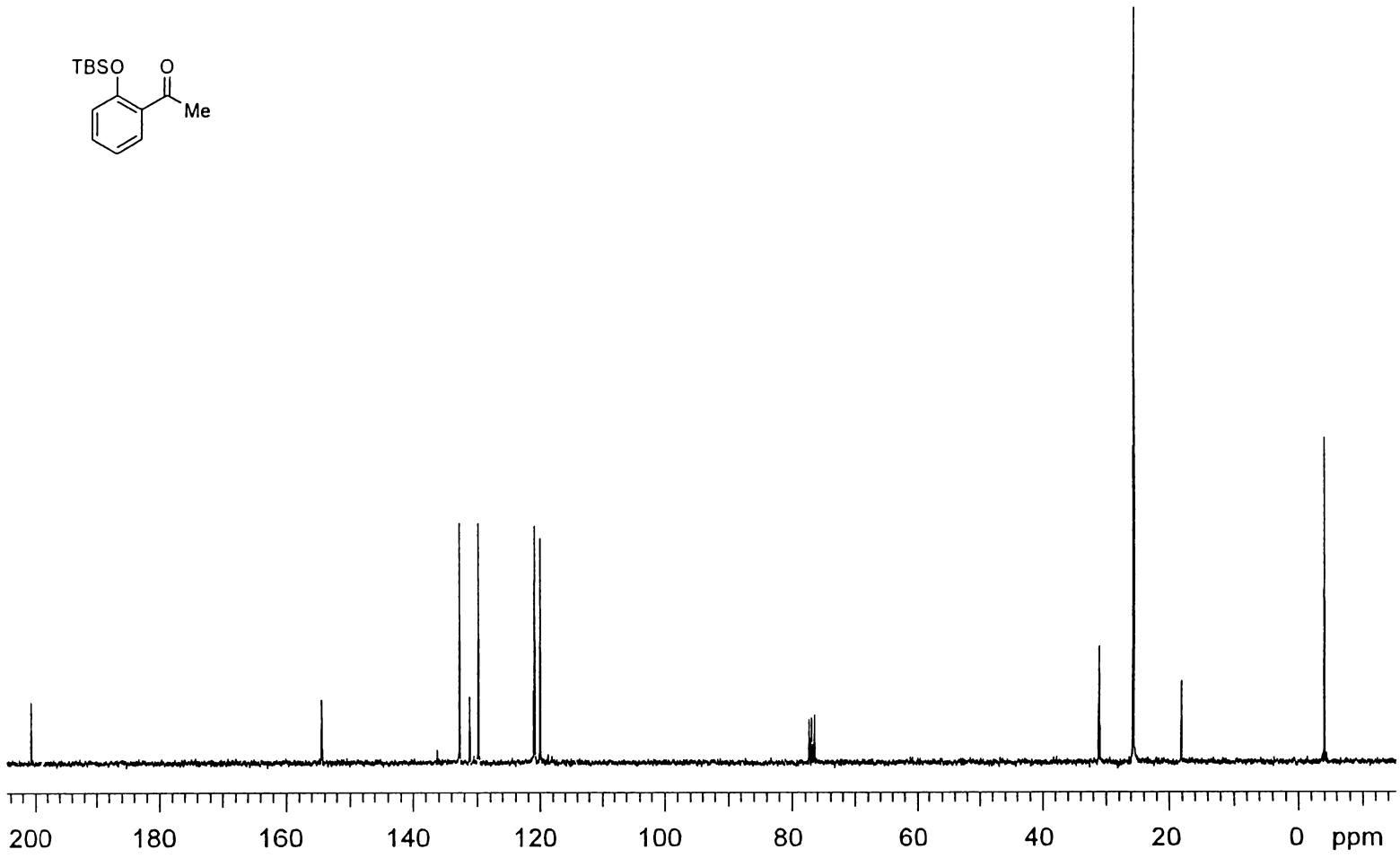
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-(*tert*-Butyldimethylsilyloxy)-6-methylbenzaldehyde (**81**).



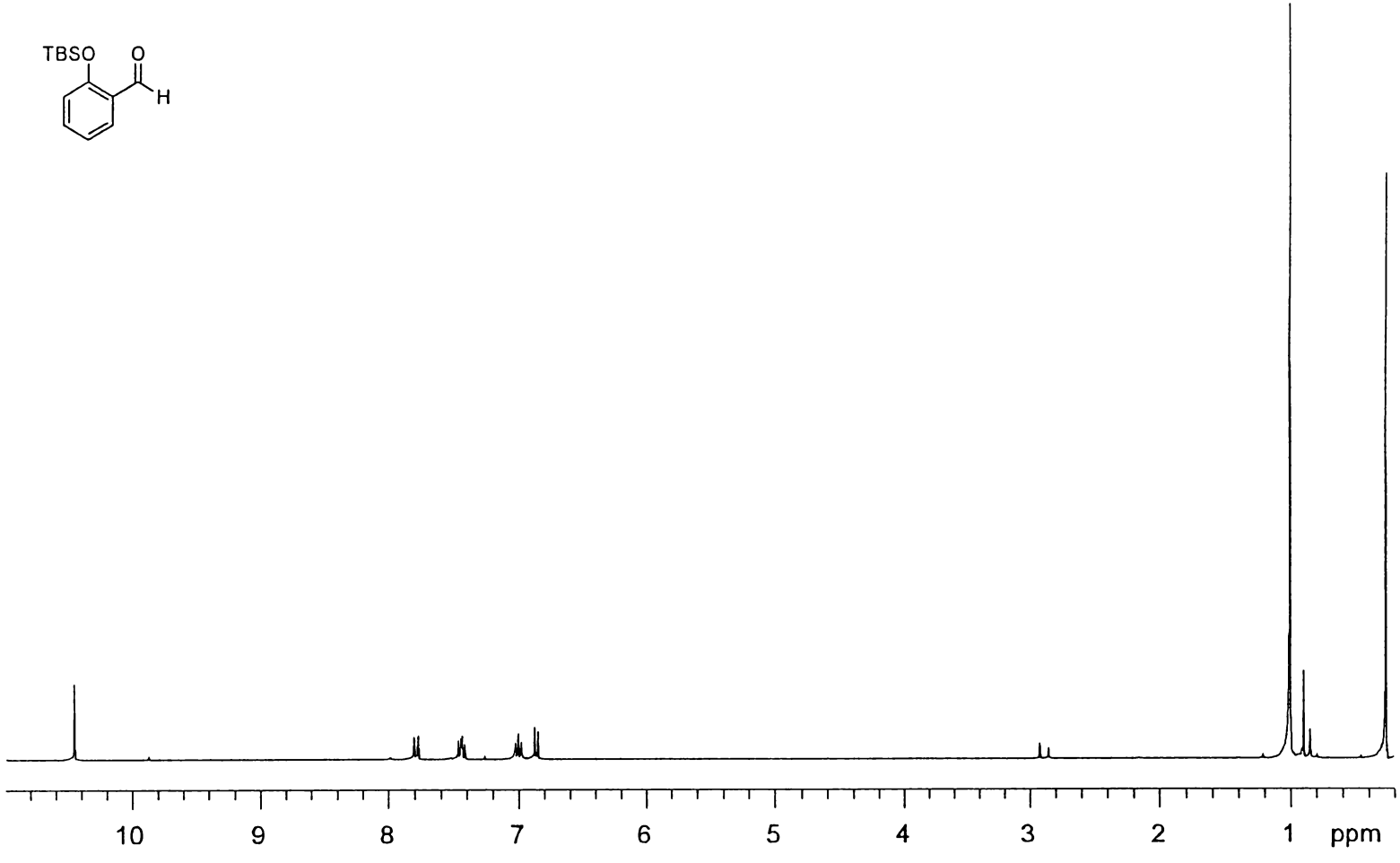
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-(*tert*-Butyldimethylsilyloxy)-6-methylbenzaldehyde (**81**).



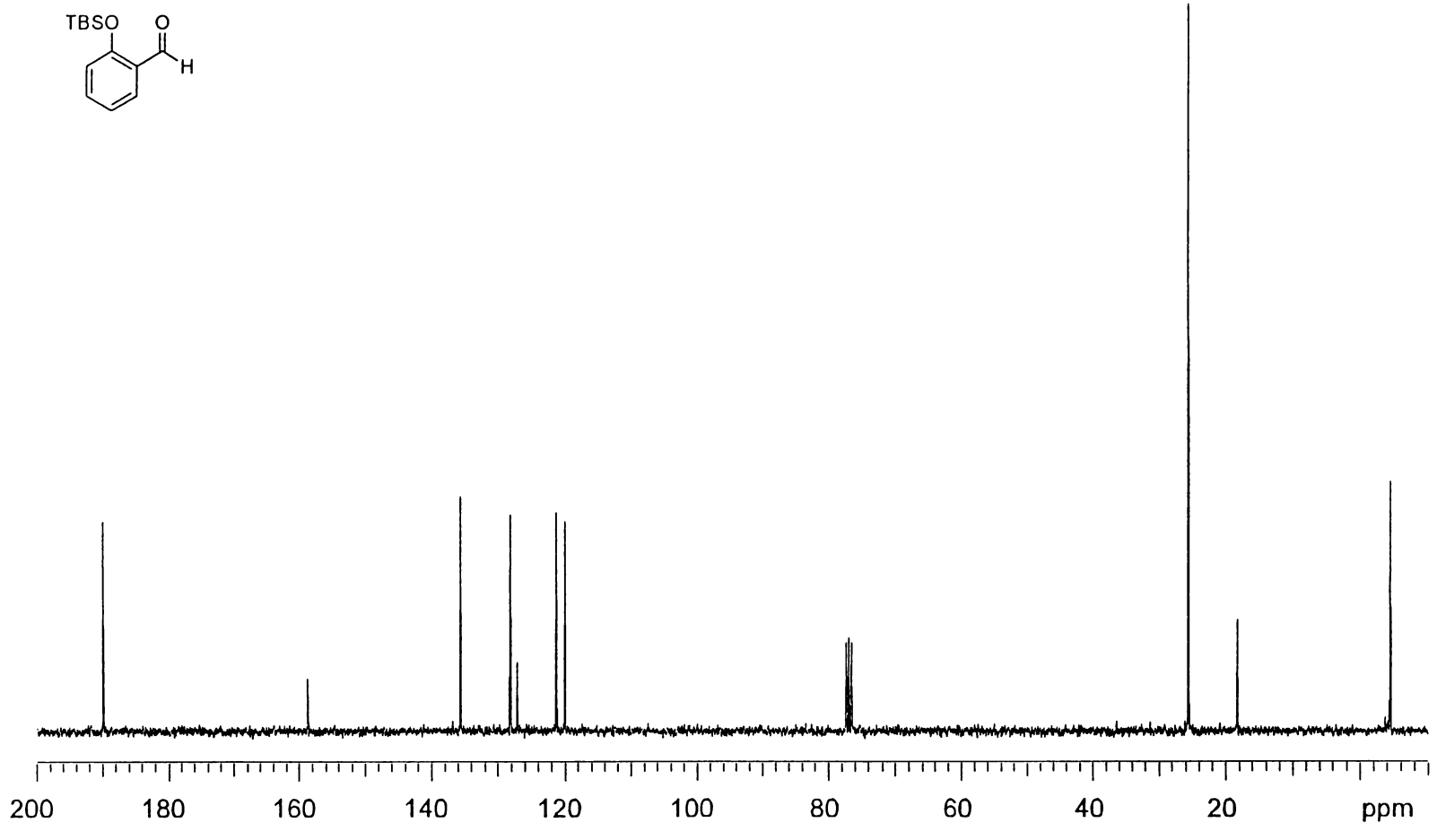
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-(2-*tert*-Butyldimethylsilyloxy)phenylethanone (**68**).



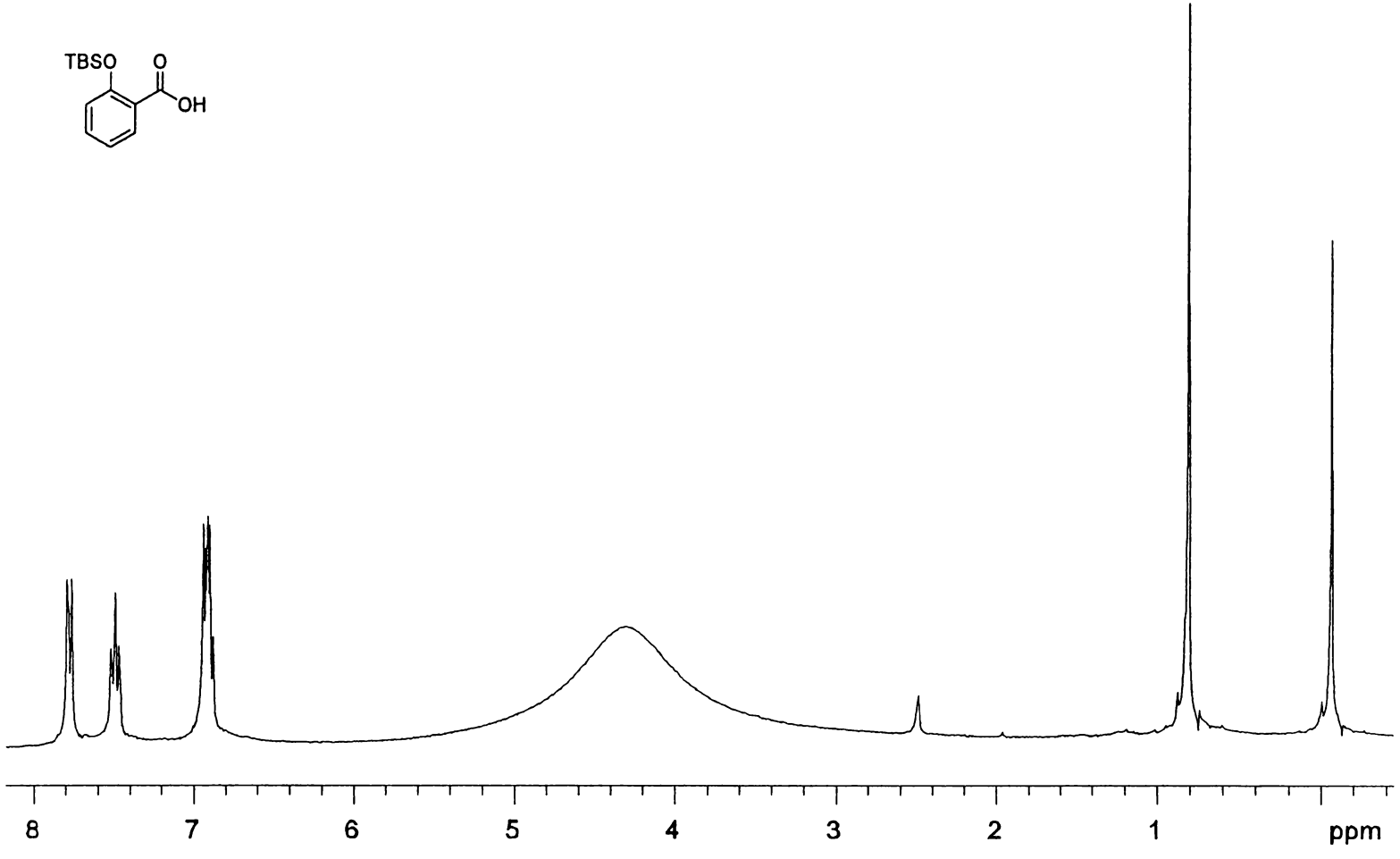
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 1-(2-*tert*-Butyldimethylsilyloxy)phenylethanone (**68**).



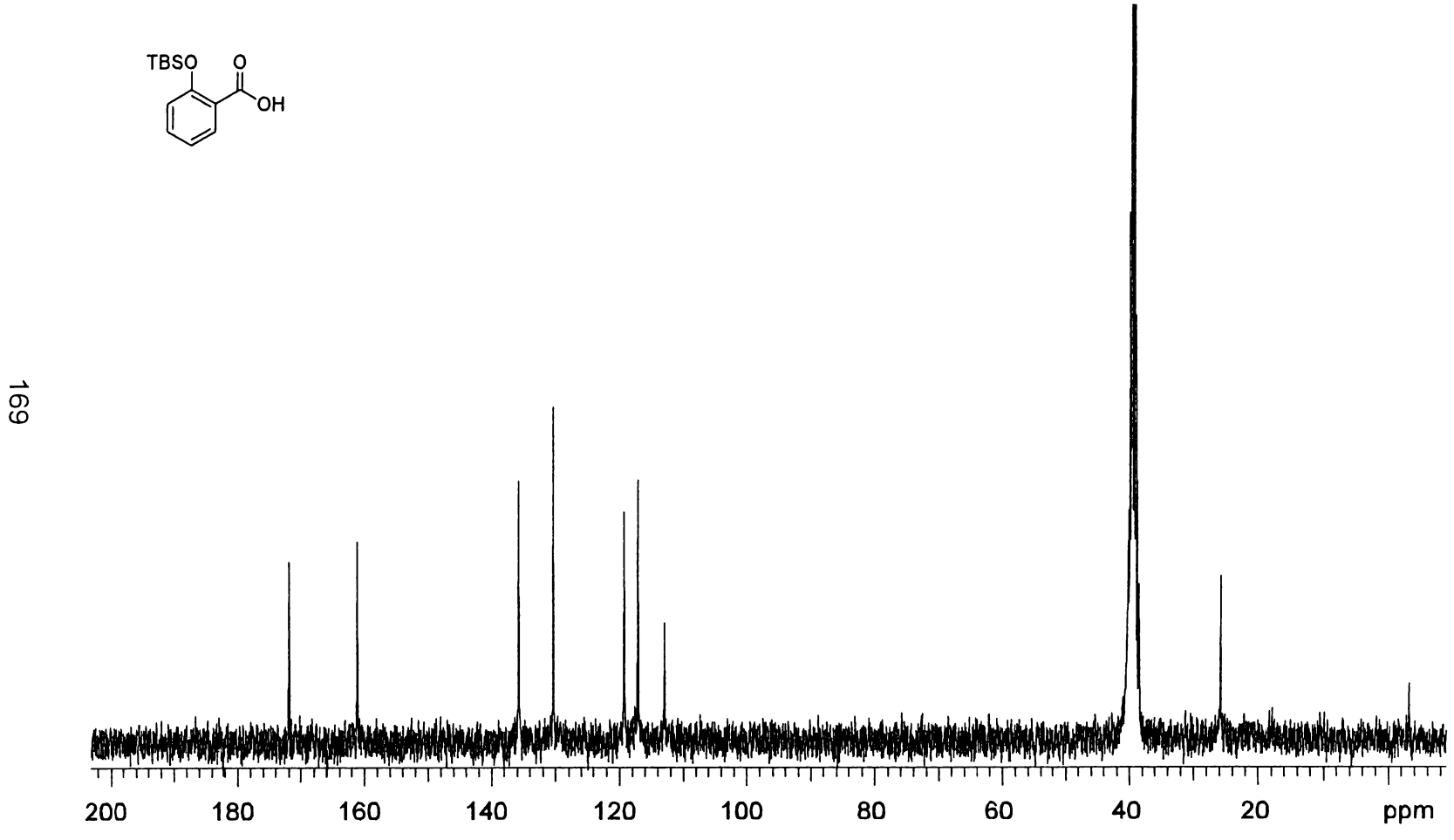
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-(*tert*-Butyldimethylsilyloxy)benzaldehyde (**79**).



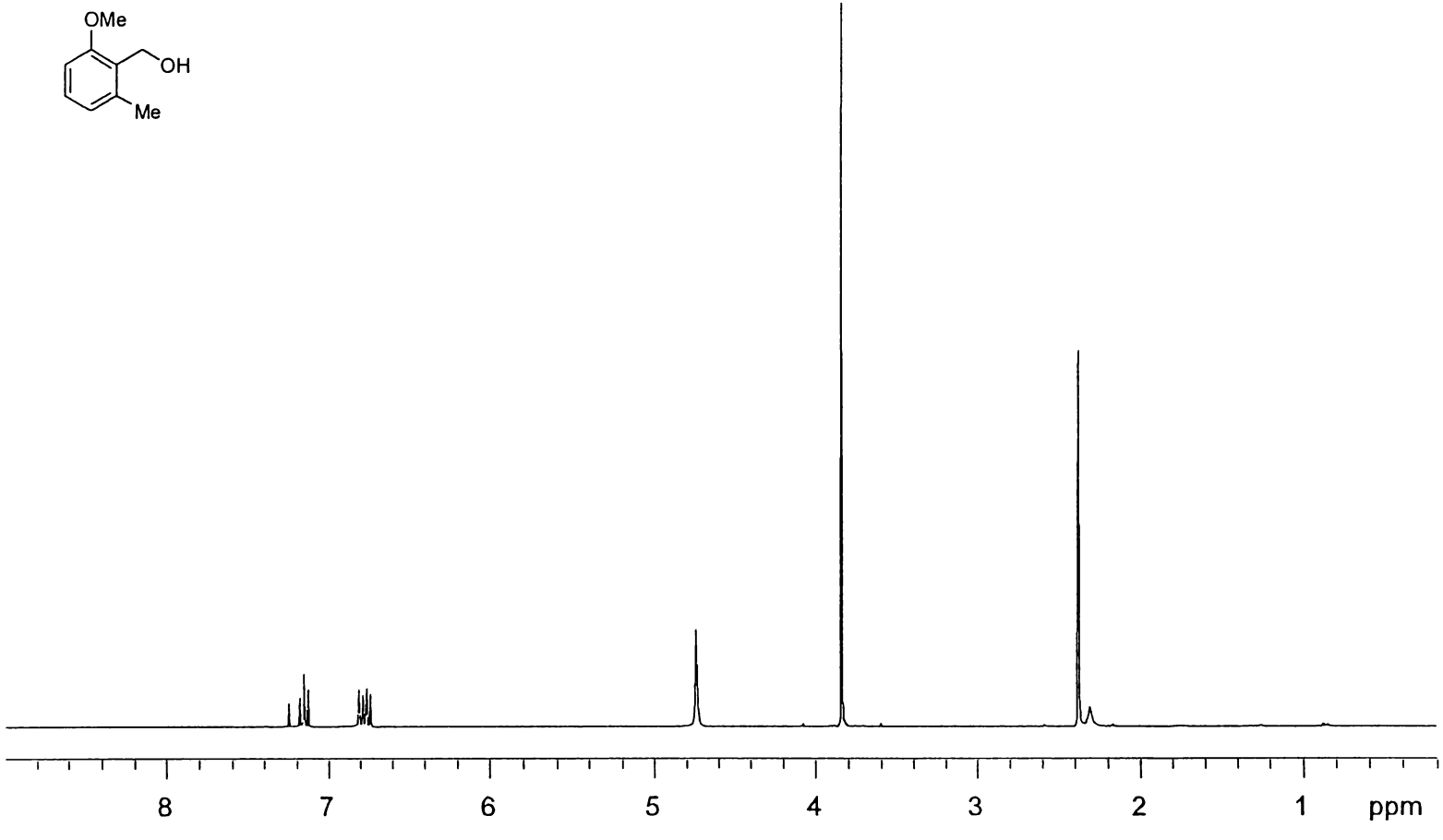
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-*(tert*-Butyldimethylsilyloxy)benzaldehyde (**79**).



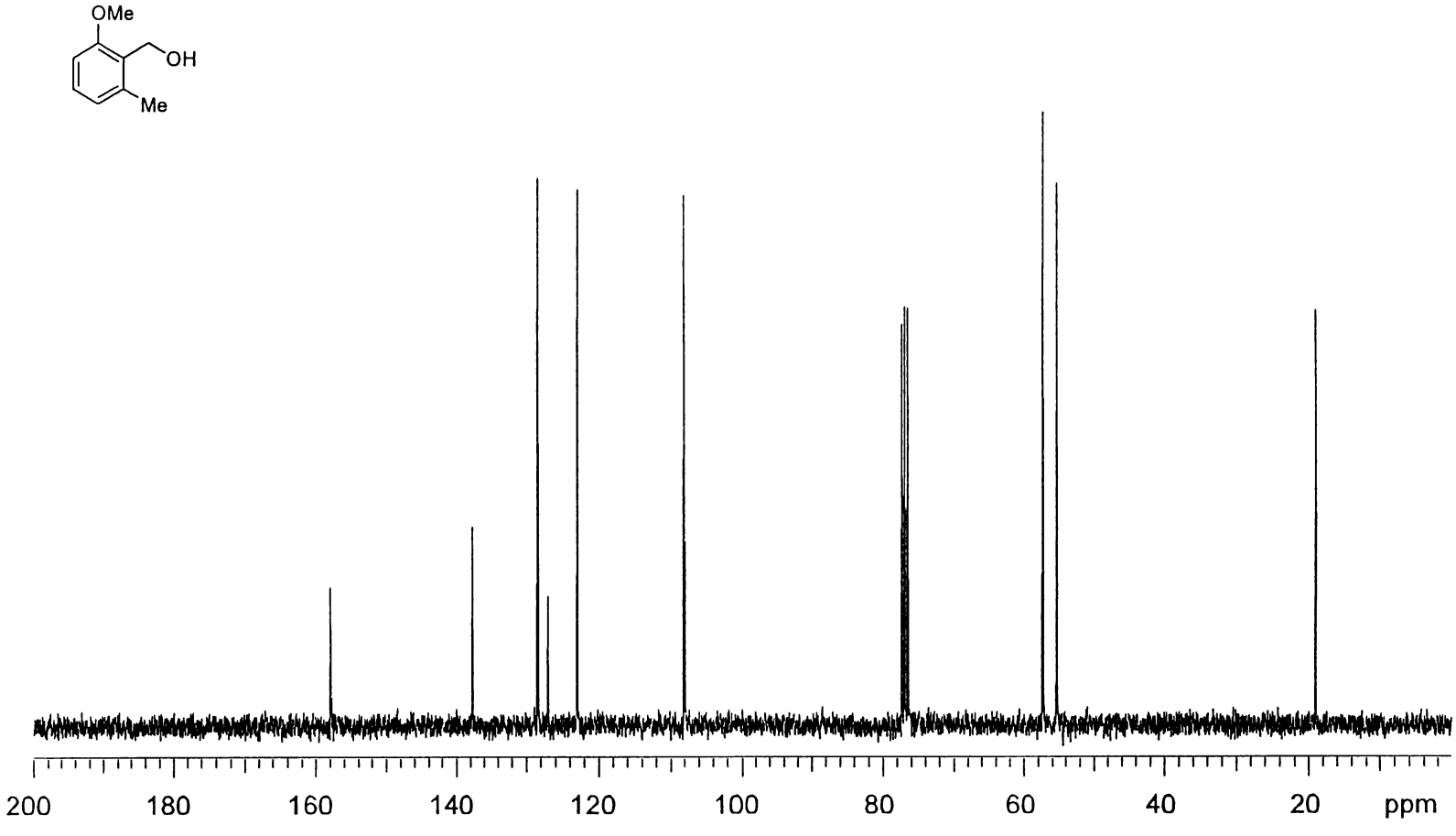
^{1}H NMR Spectrum (300 MHz, DMSO-d_6) of 2-*tert*-Butyldimethylsiyloxybenzoic Acid (**89**).



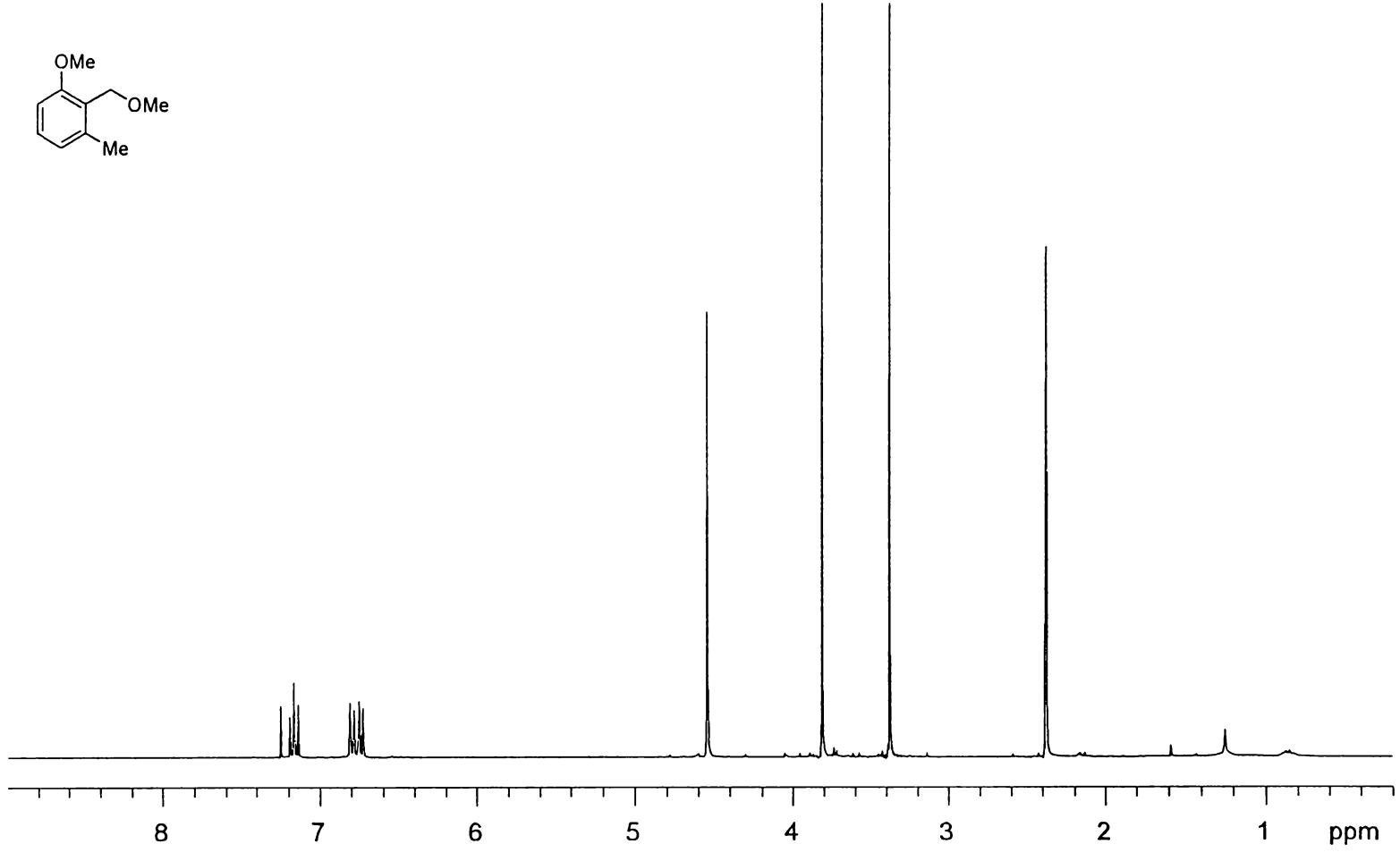
^{13}C NMR Spectrum (75 MHz, DMSO-d_6) of 2-*tert*-Butyldimethylsilyloxybenzoic Acid (**89**).



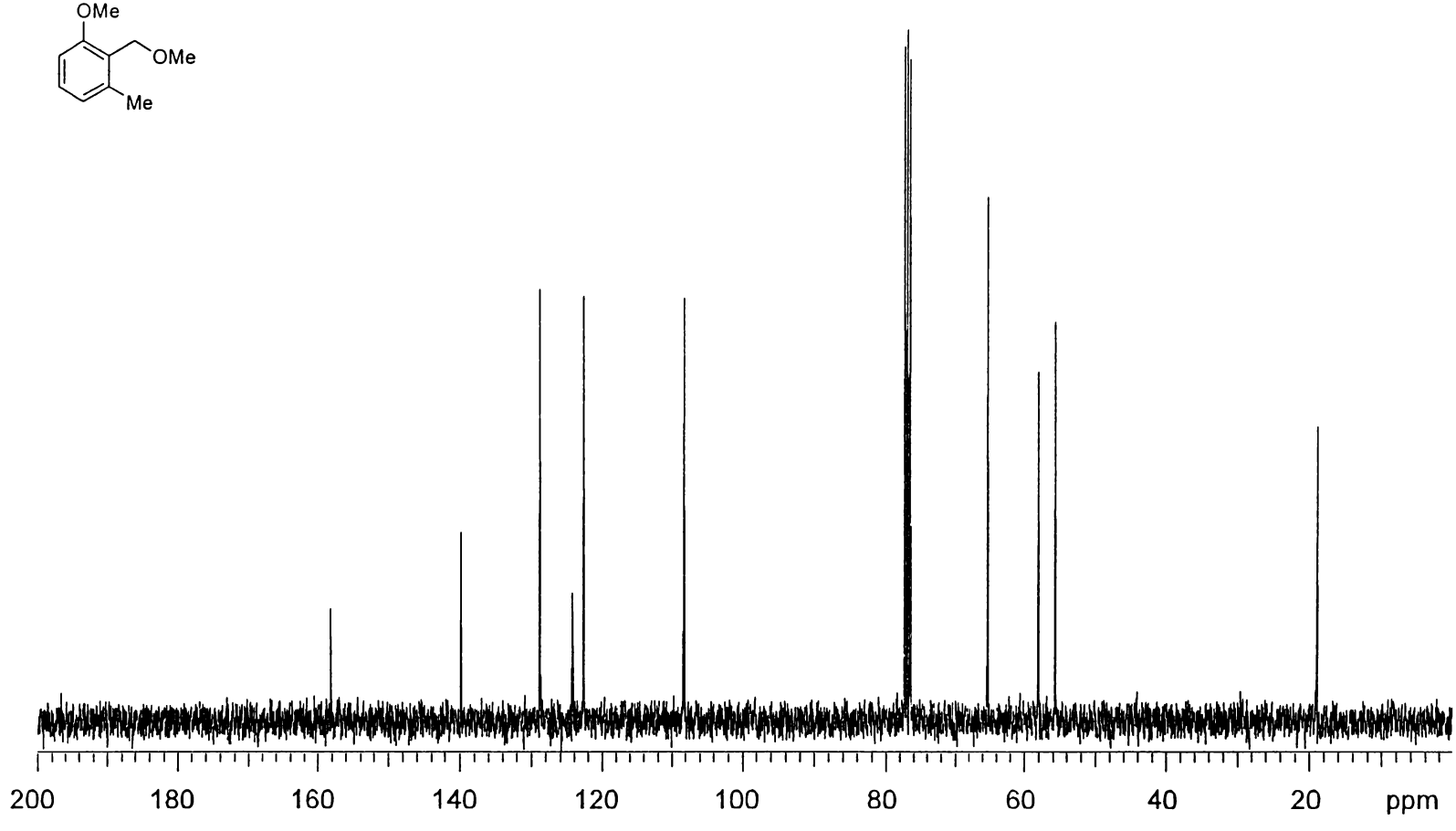
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of (2-Methoxy-6-methylphenyl)methanol (**42**).



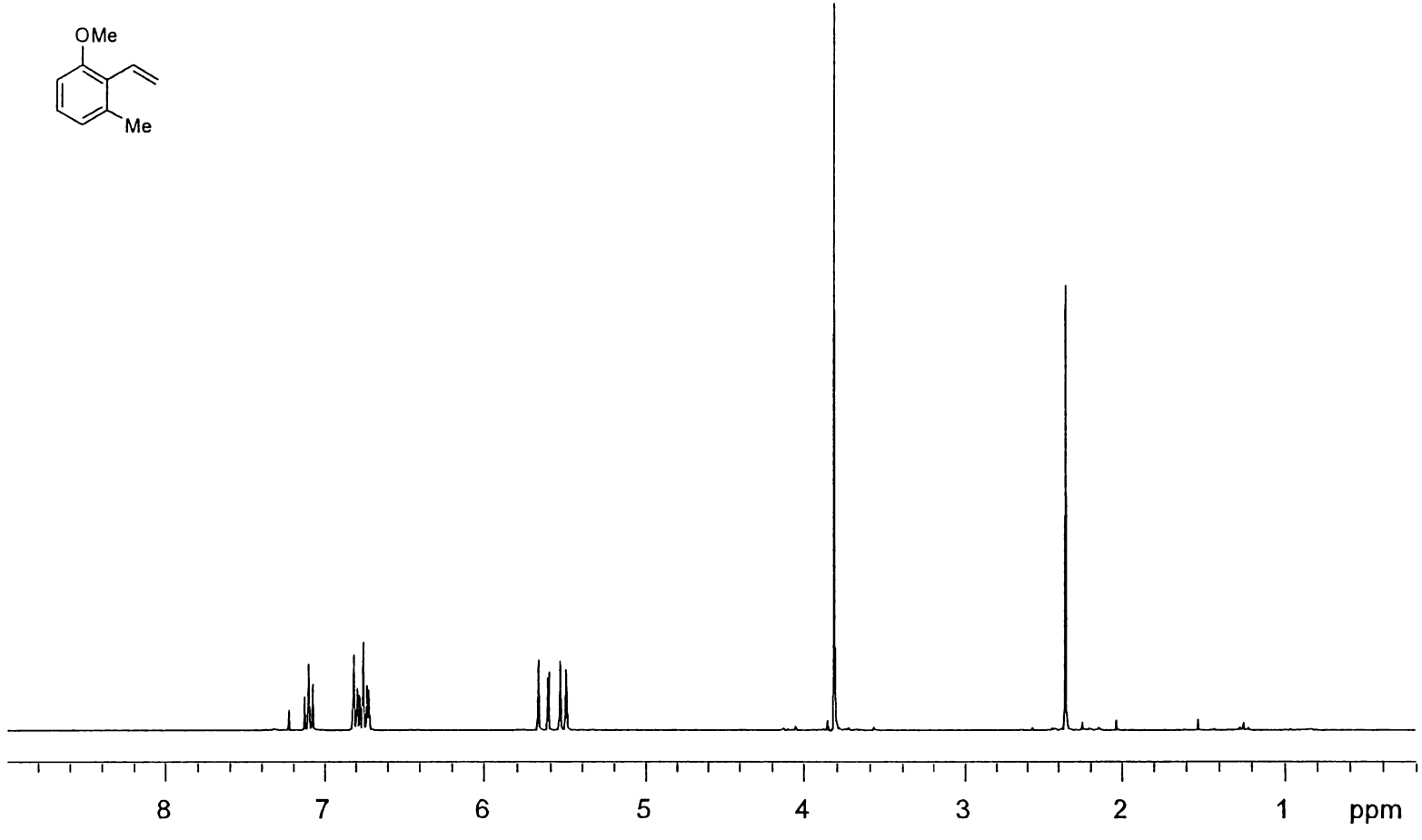
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of (2-Methoxy-6-methylphenyl)methanol (**42**).



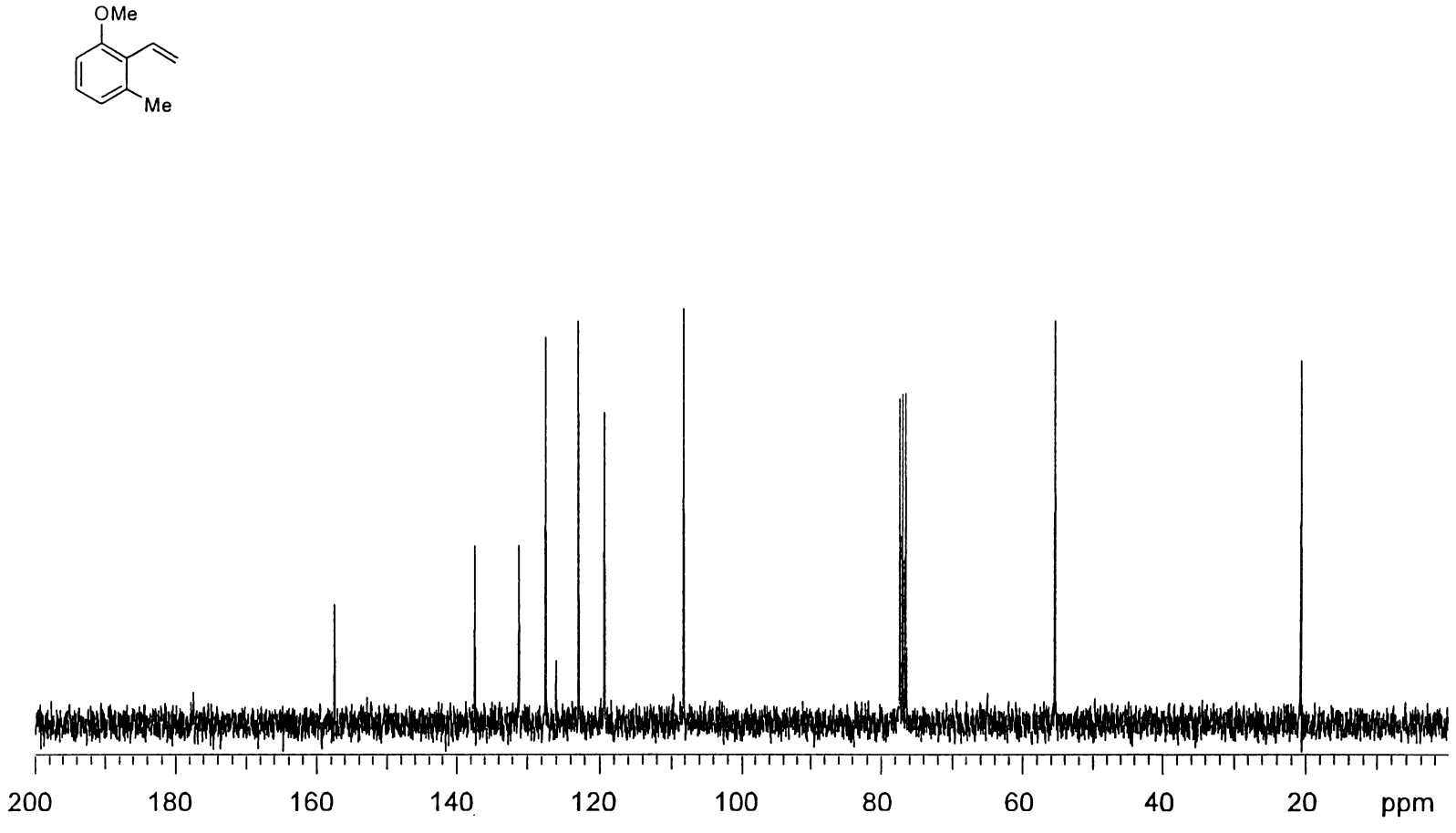
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Methoxymethyl-3-methylanisole (**43**).



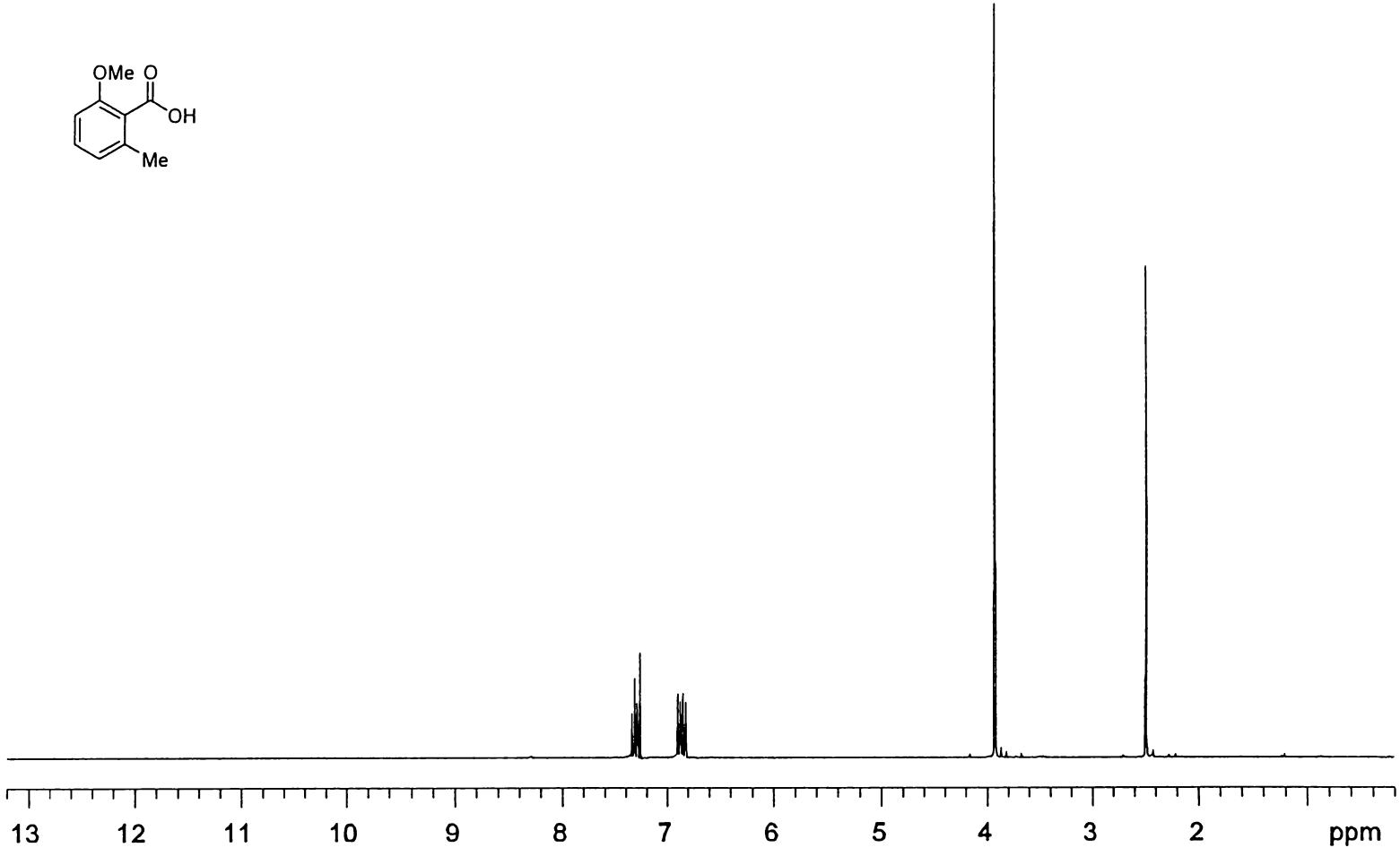
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Methoxymethyl-3-methylanisole (**43**).



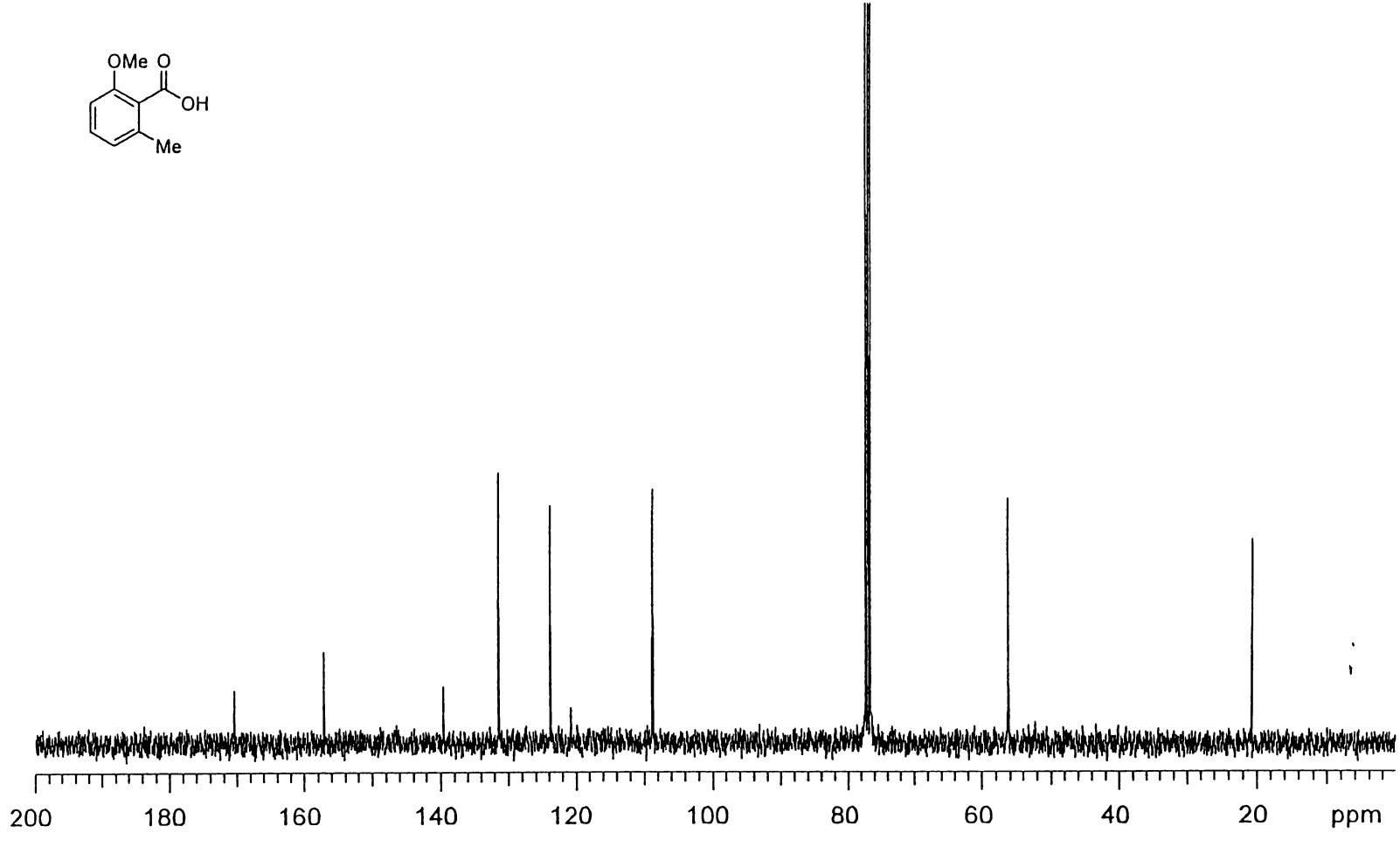
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 3-Methyl-2-vinylanisole (**41**).



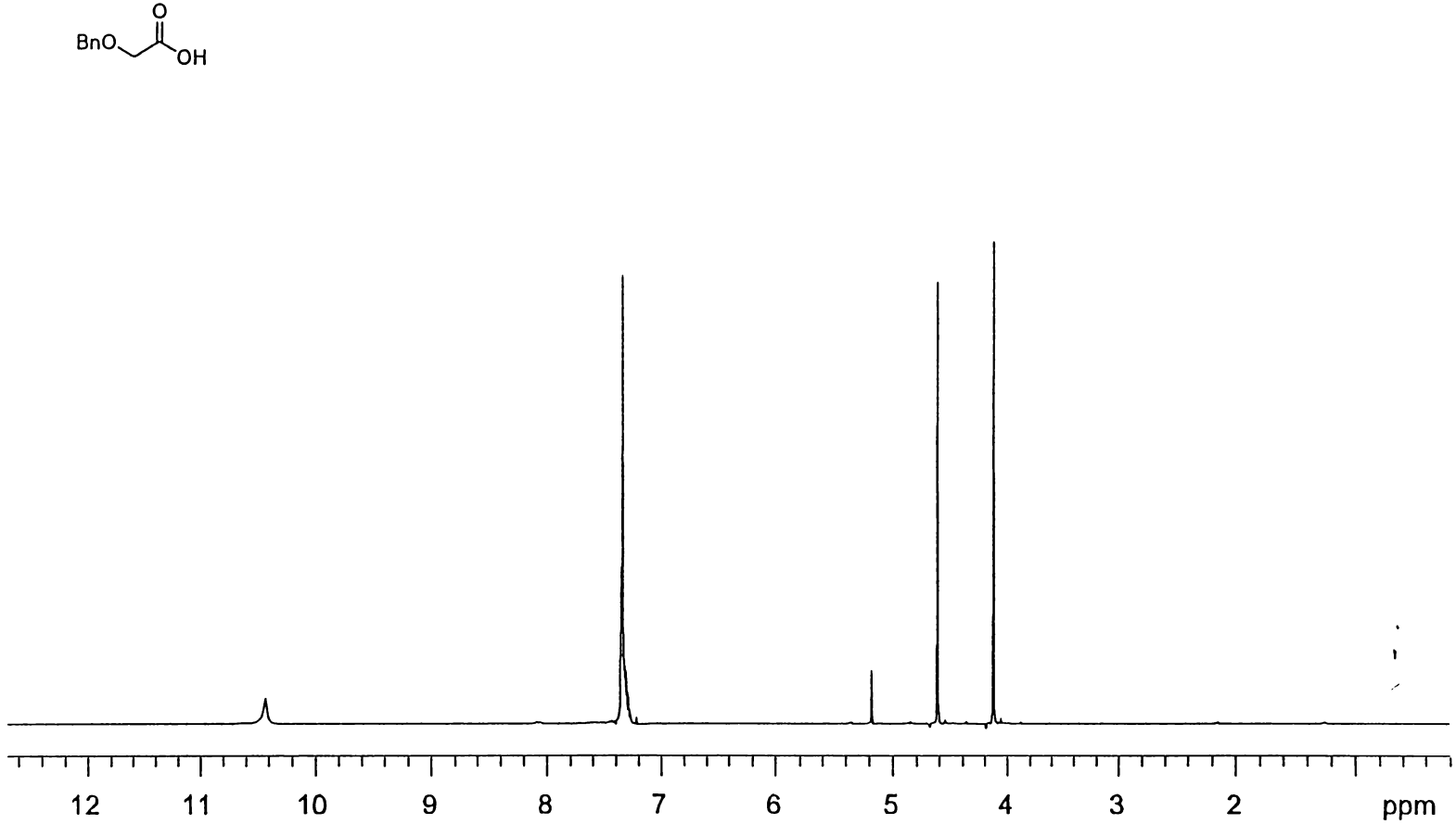
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 3-Methyl-2-vinylanisole (**41**).



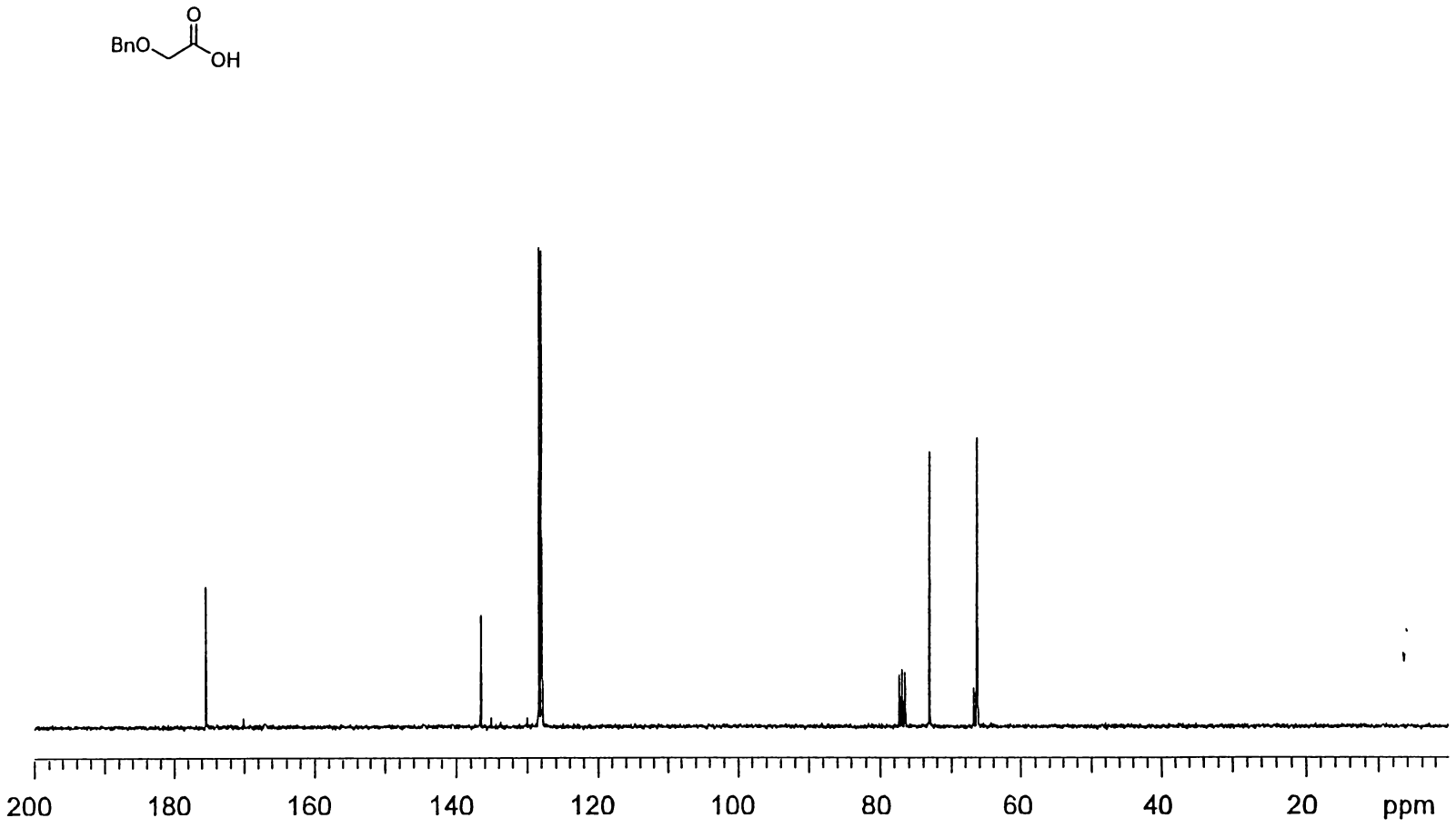
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Methoxy-6-methylbenzoic Acid (**44**).



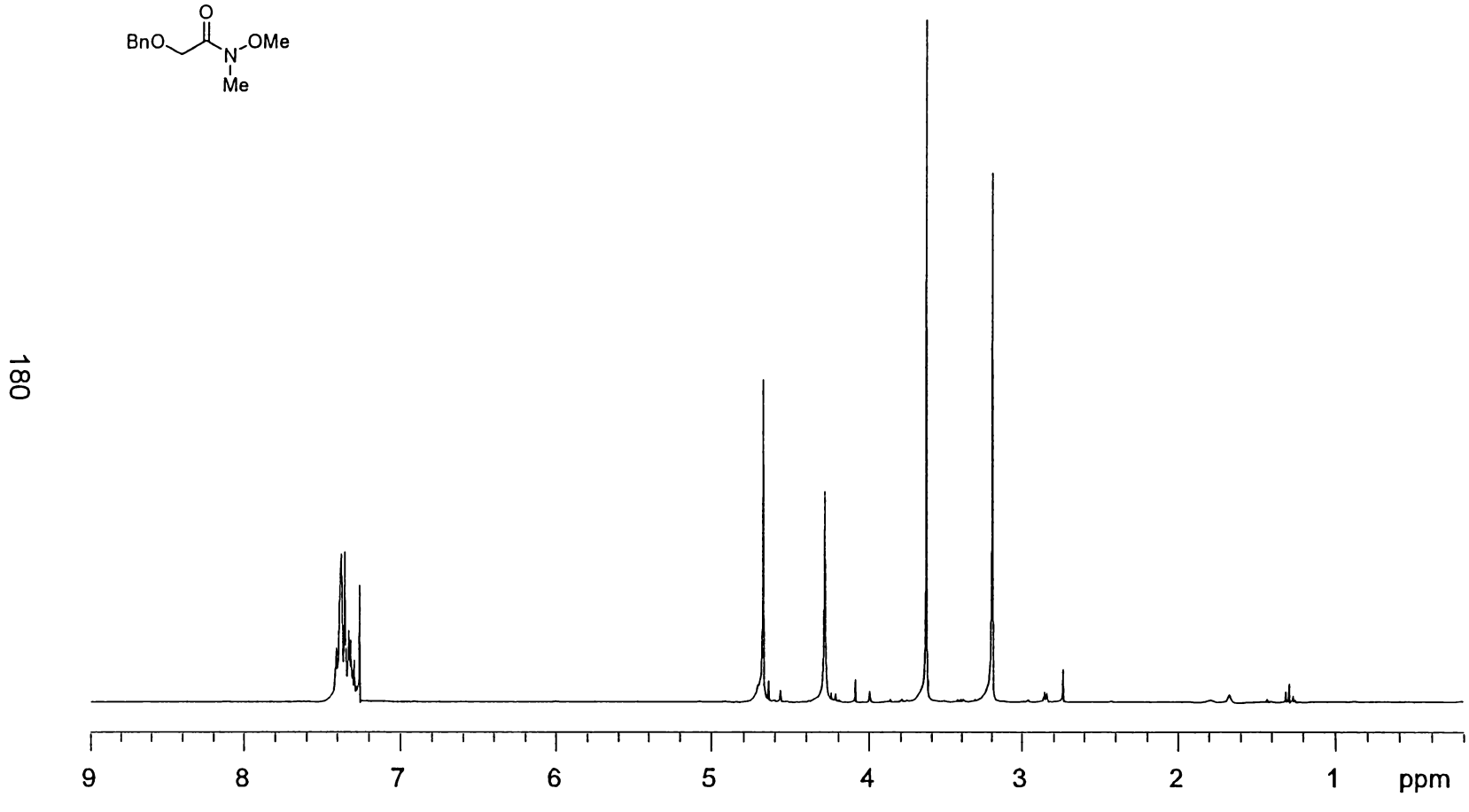
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Methoxy-6-methylbenzoic Acid (**44**).



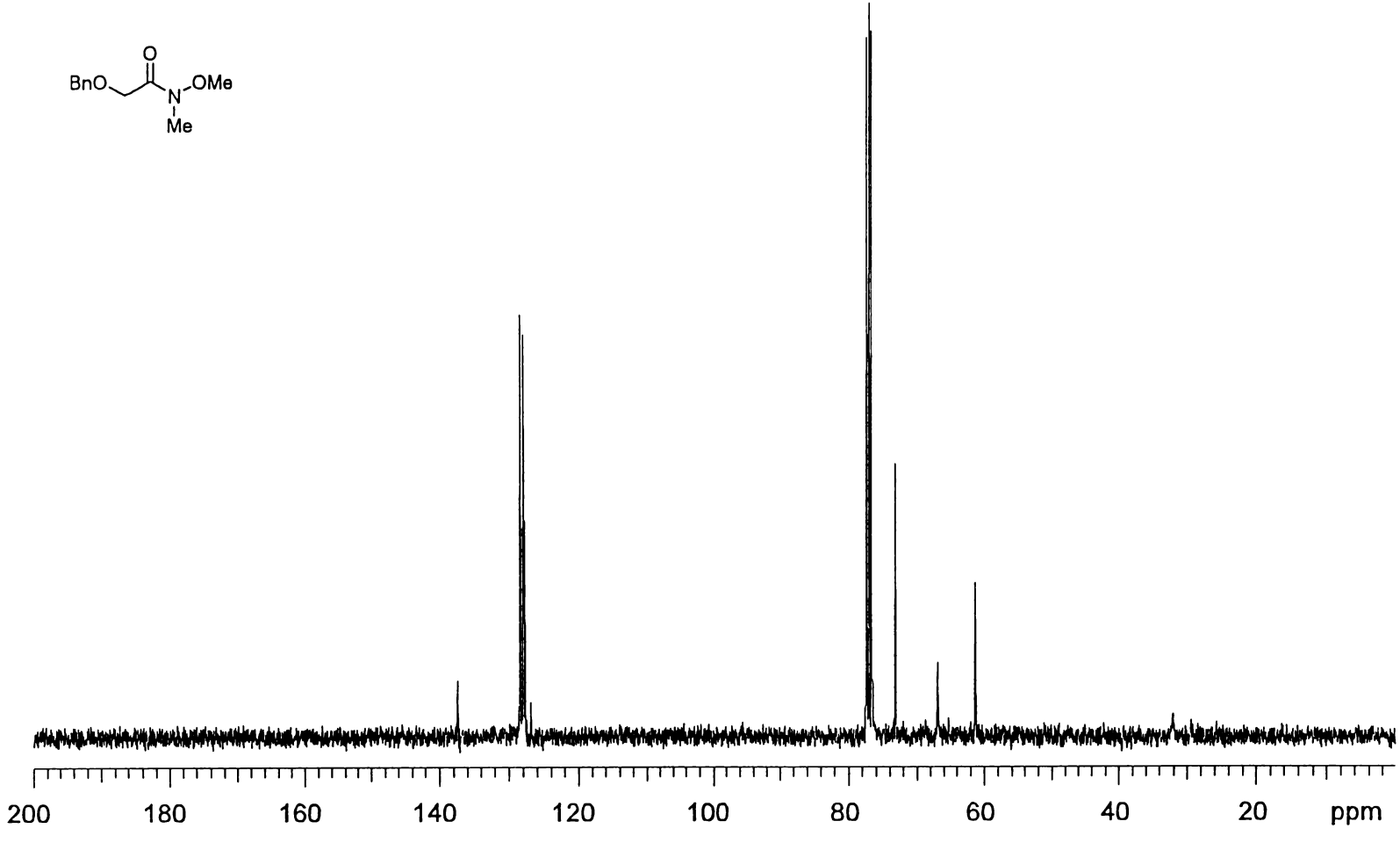
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of Benzyloxyacetic Acid (**63**).



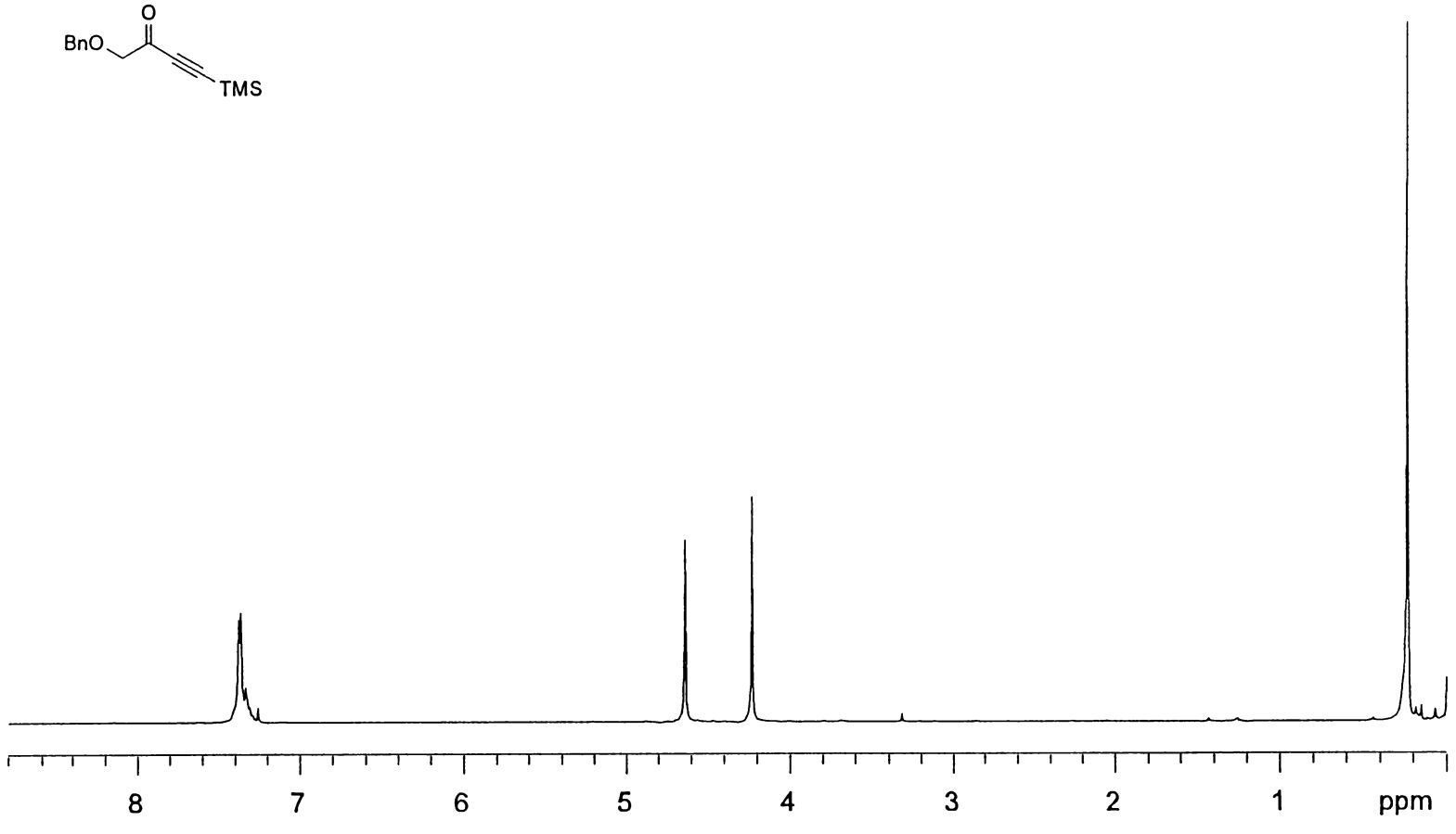
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of Benzyloxyacetic Acid (**63**).



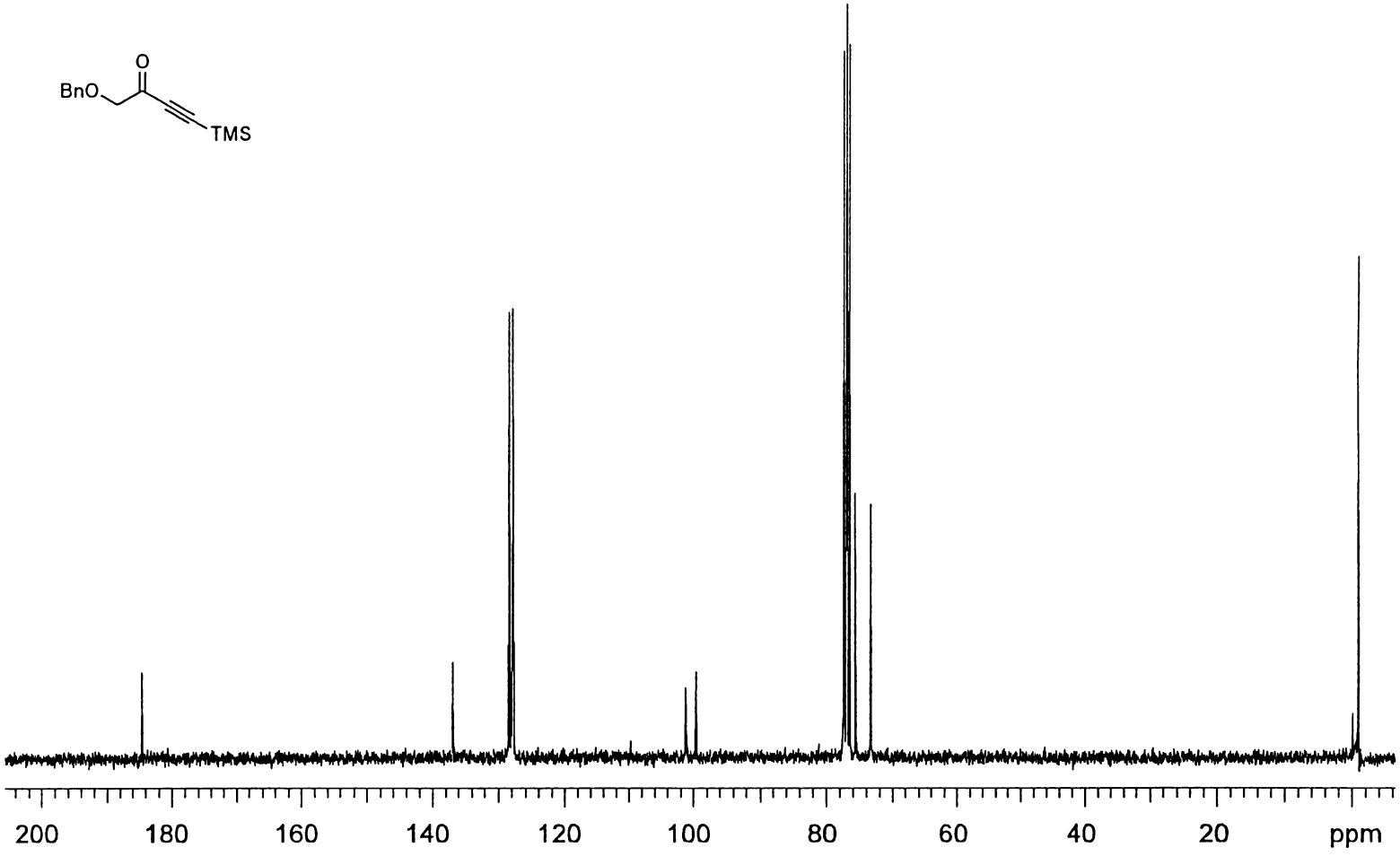
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-Benxyloxy-*N*-methoxy-*N*-methylacetamide (**64**).



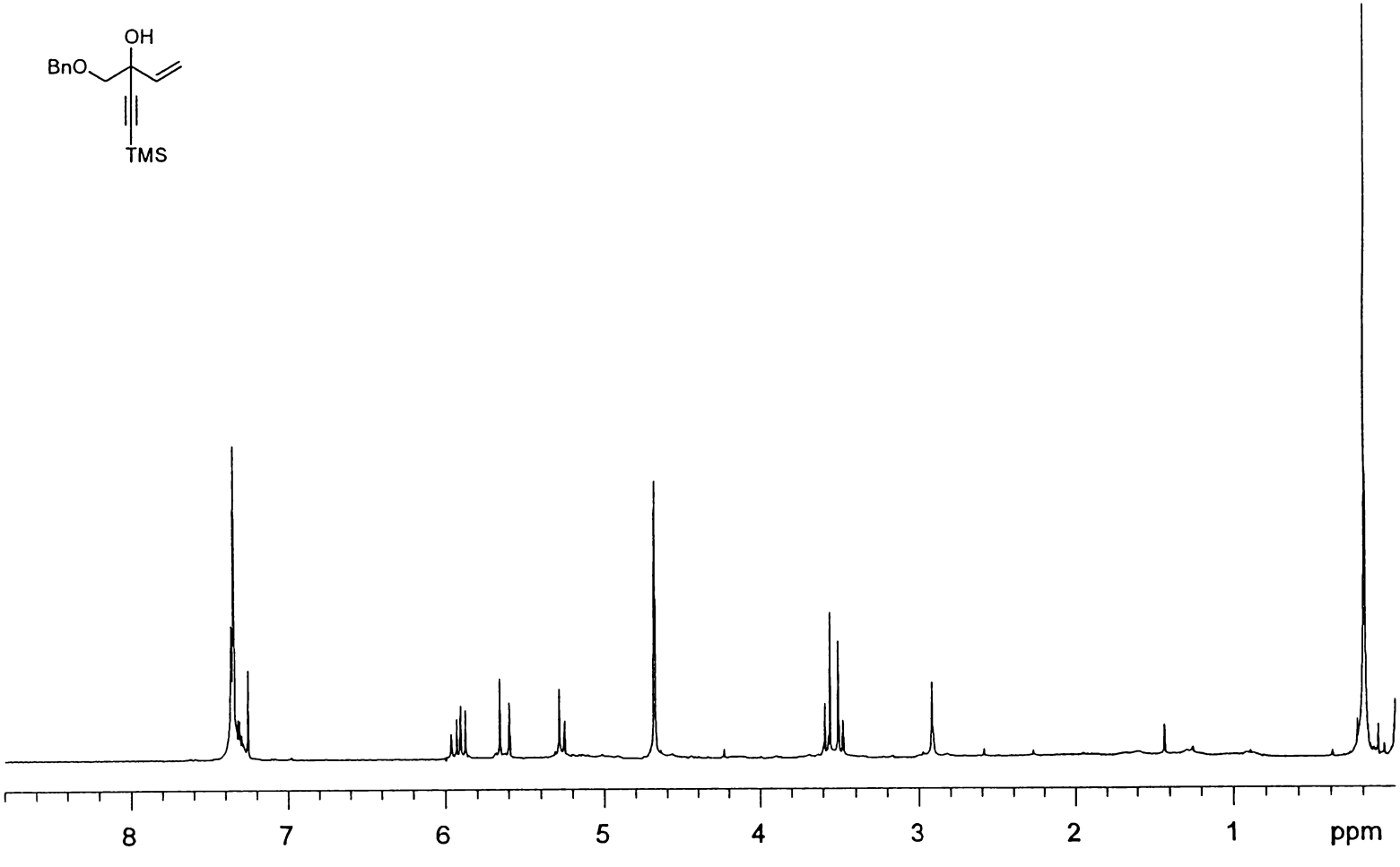
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-Benxyloxy-*N*-methoxy-*N*-methylacetamide (**64**).



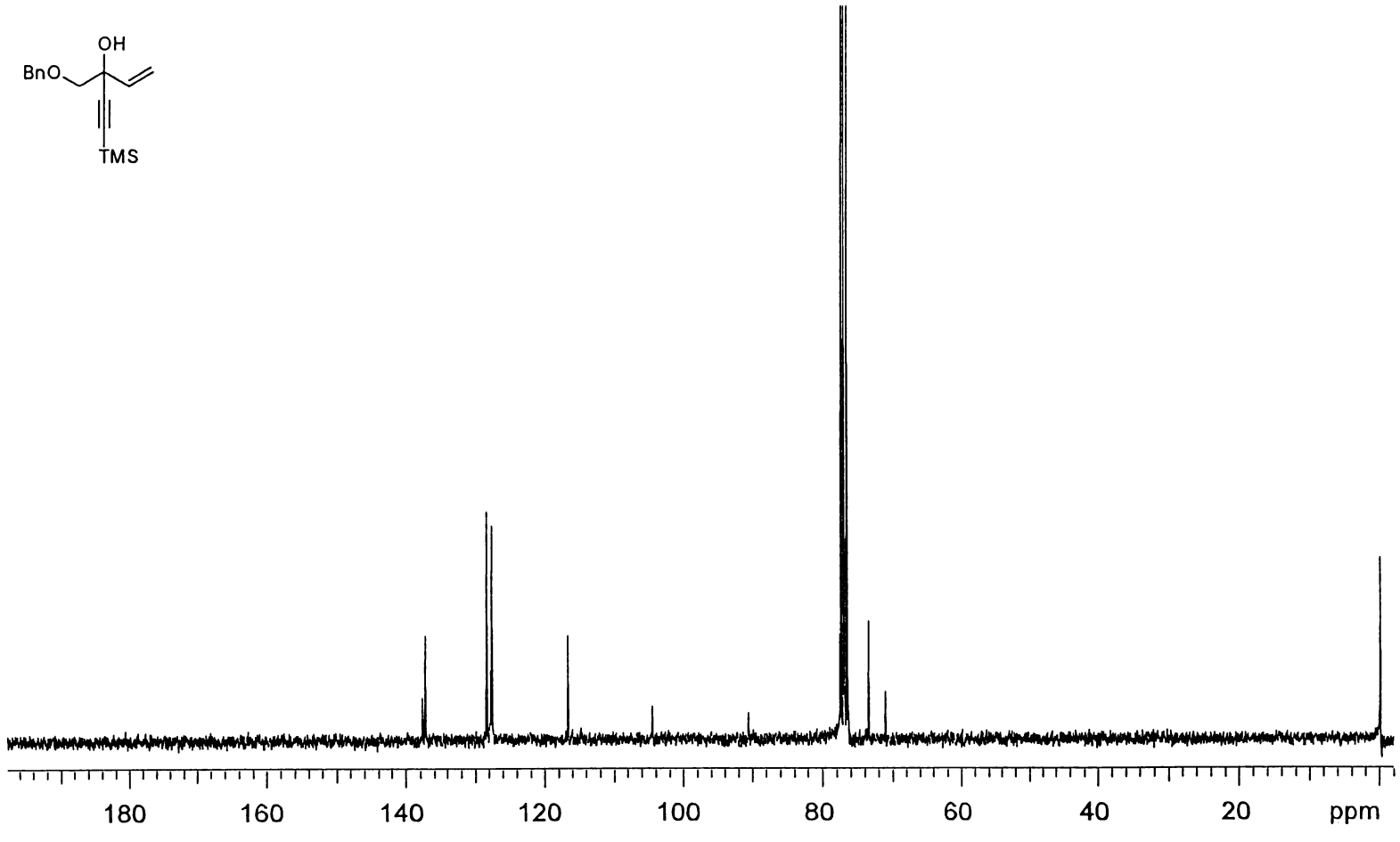
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 1-Benzyloxy-4-trimethylsilyl-but-3-yn-2-one (**65**).



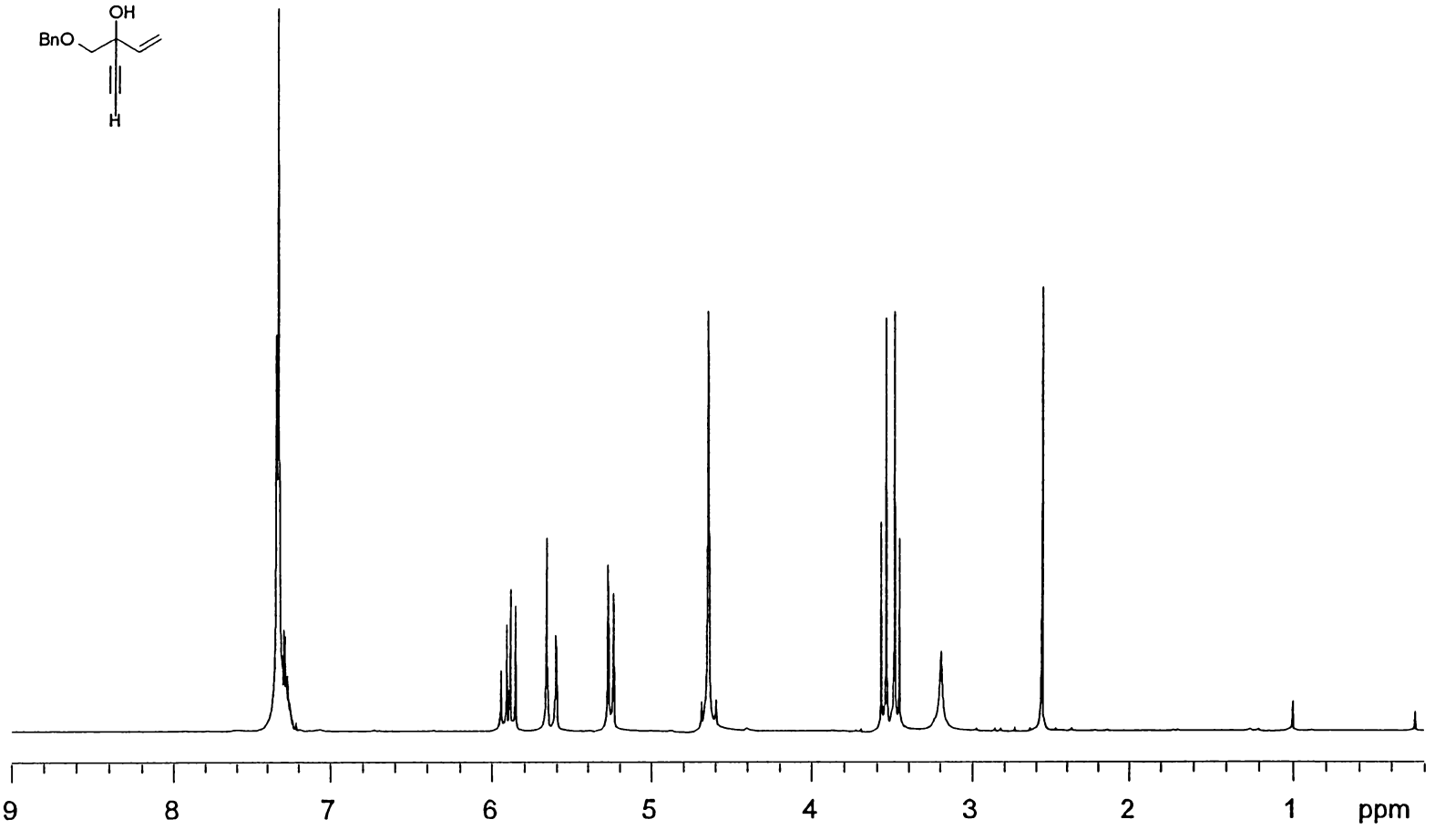
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 1-Benzyloxy-4-trimethylsilyl-but-3-yn-2-one (**65**).



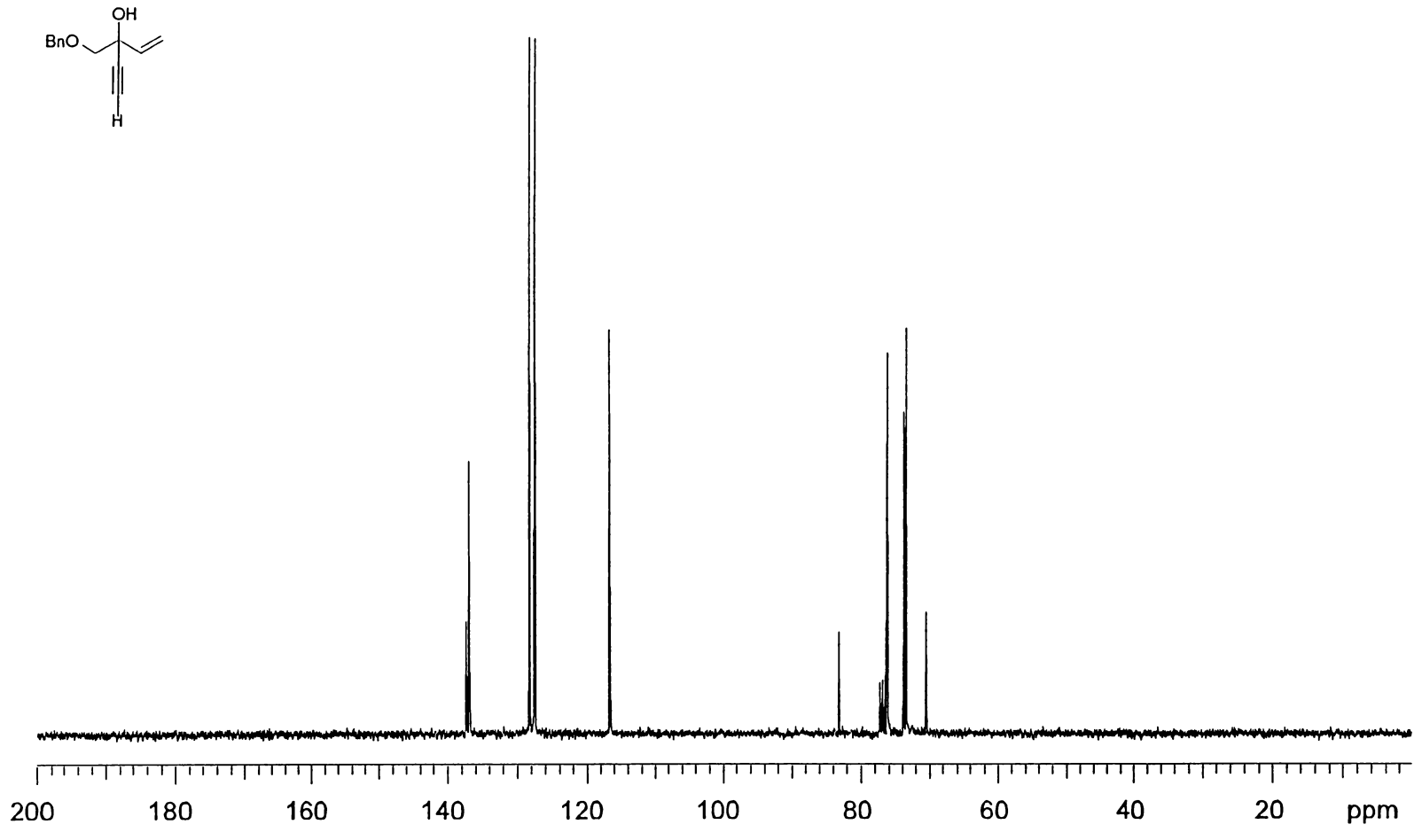
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 3-Benzyloxymethyl-5-trimethylsilanyl-pent-1-en-4-yn-3-ol (**66**).



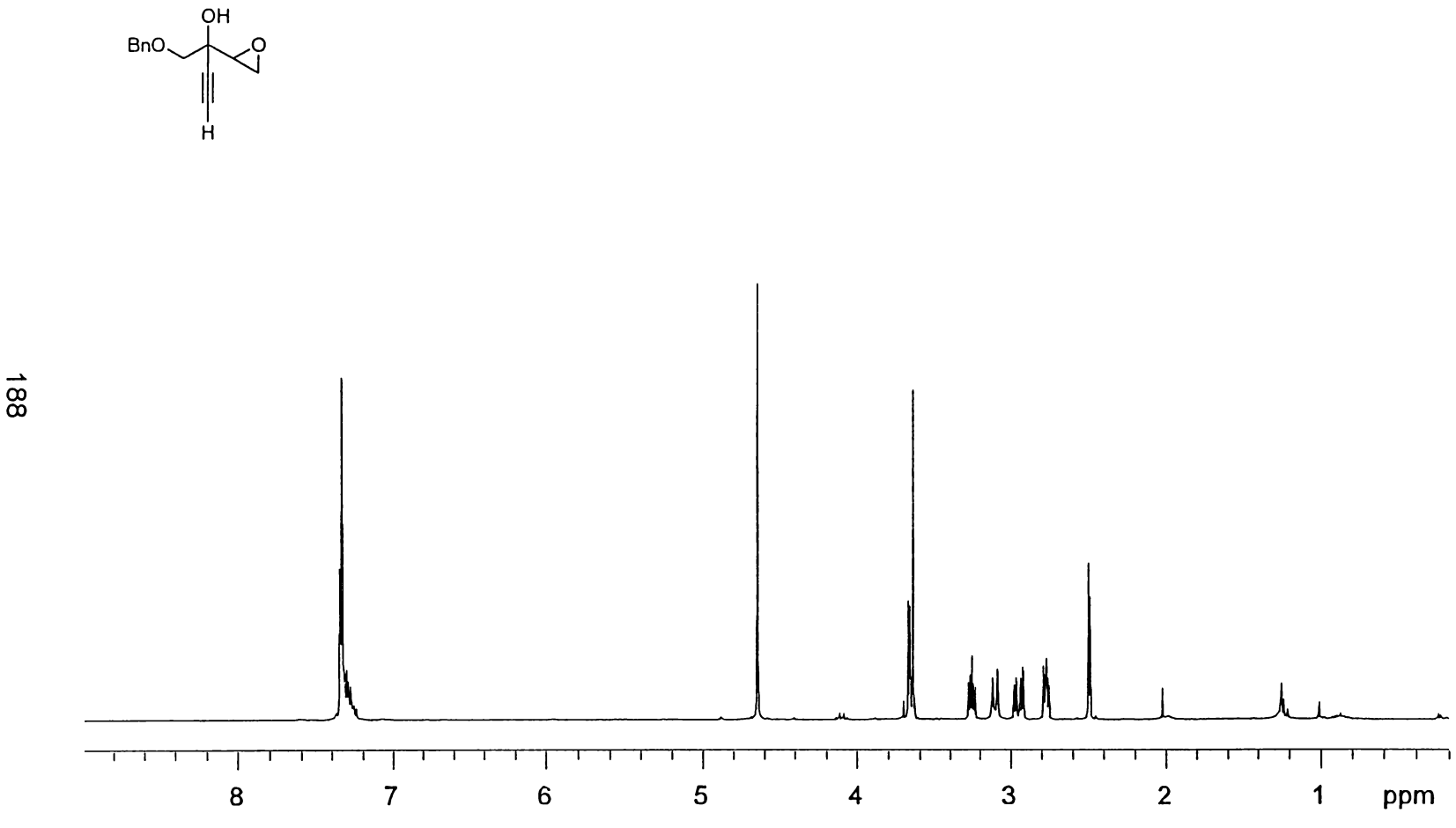
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 3-Benzyloxymethyl-5-trimethylsilanyl-pent-1-en-4-yn-3-ol (**66**).



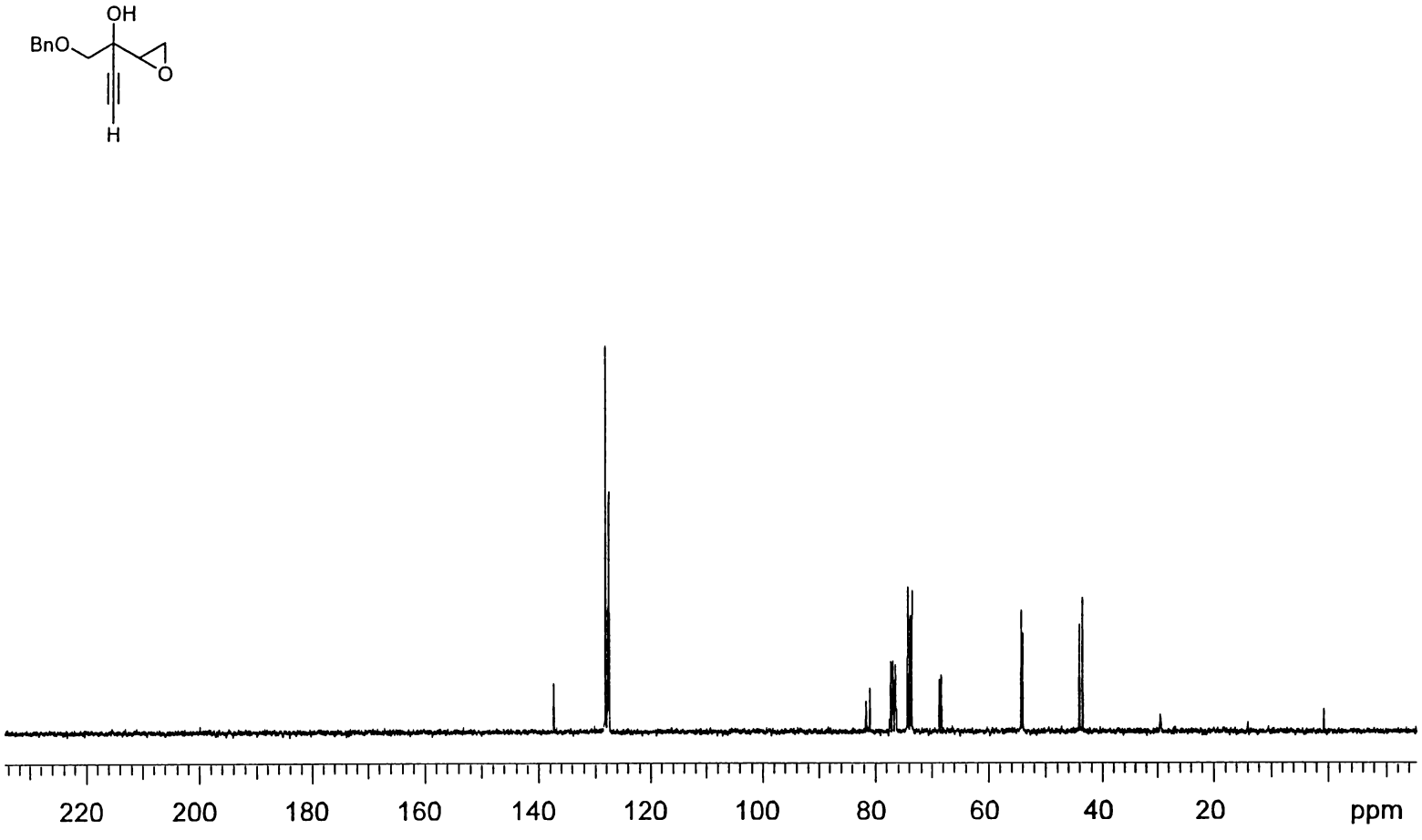
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 3-Benzyloxymethyl-pent-1-en-4-yn-3-ol (**67**).



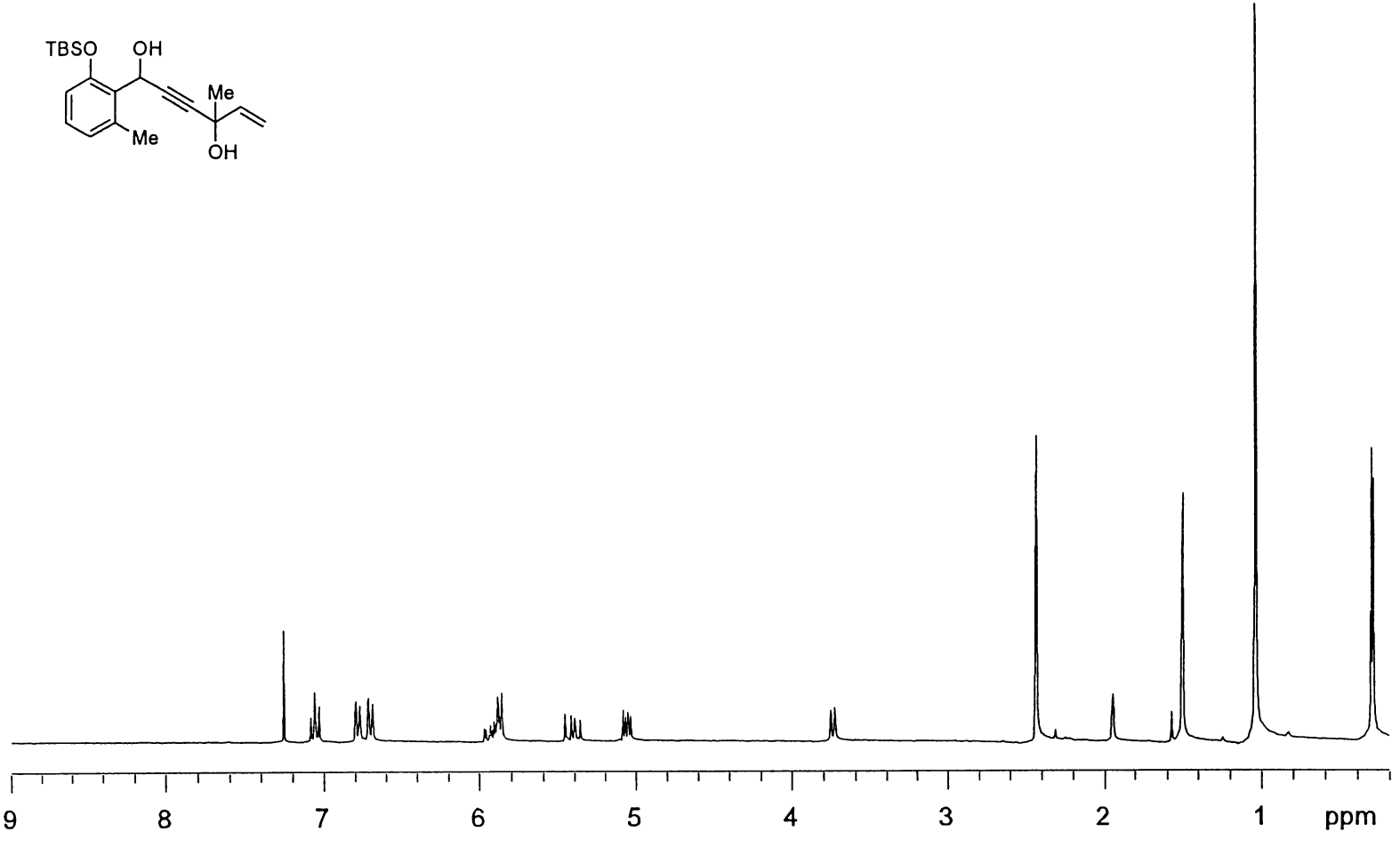
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 3-Benzyloxymethyl-pent-1-en-4-yn-3-ol (**67**).



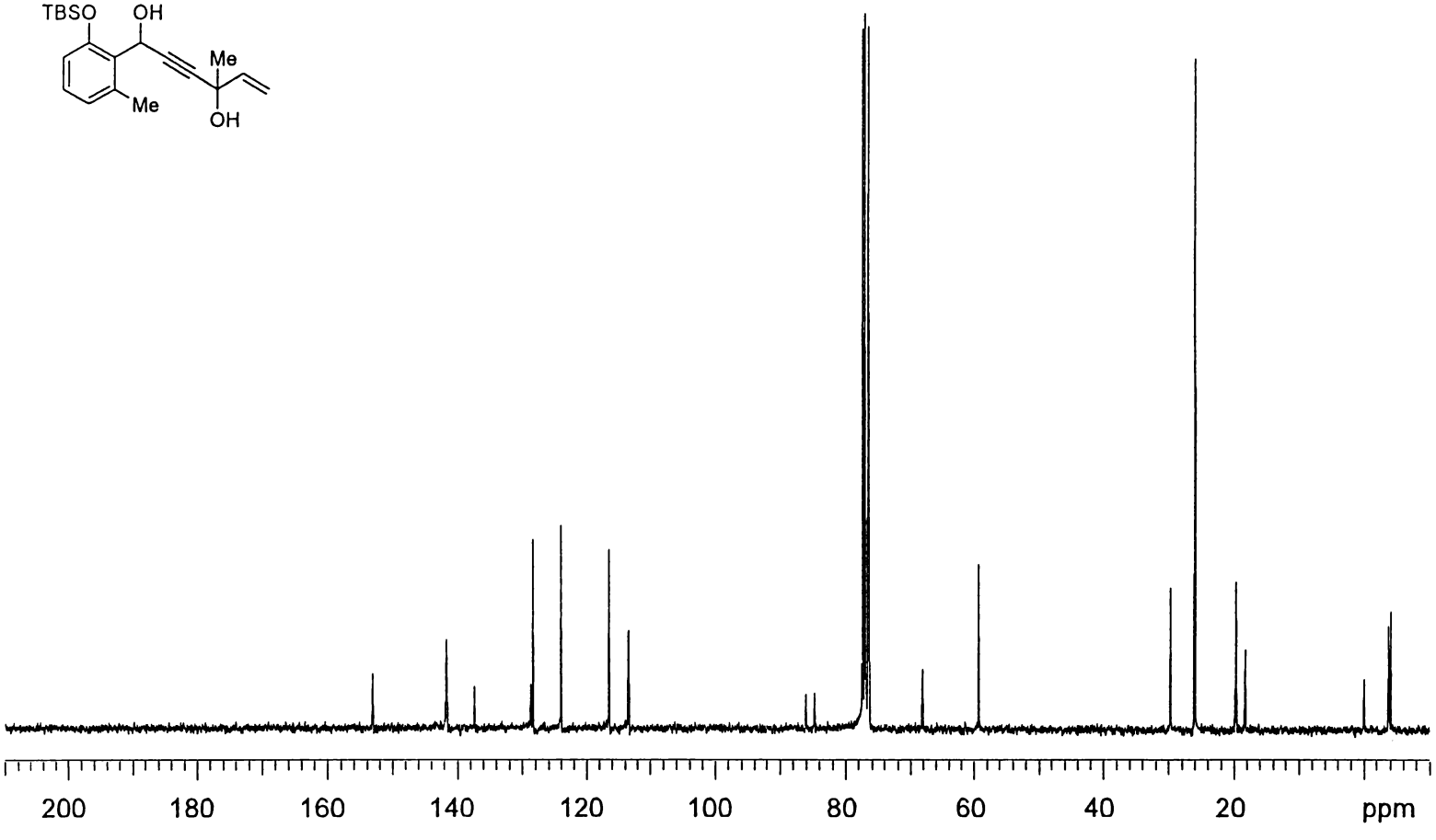
^{1}H NMR Spectrum (300 MHz, CDCl3) of 1-Benzyloxy-2-oxiranyl-but-3-yn-2-ol (**87**).



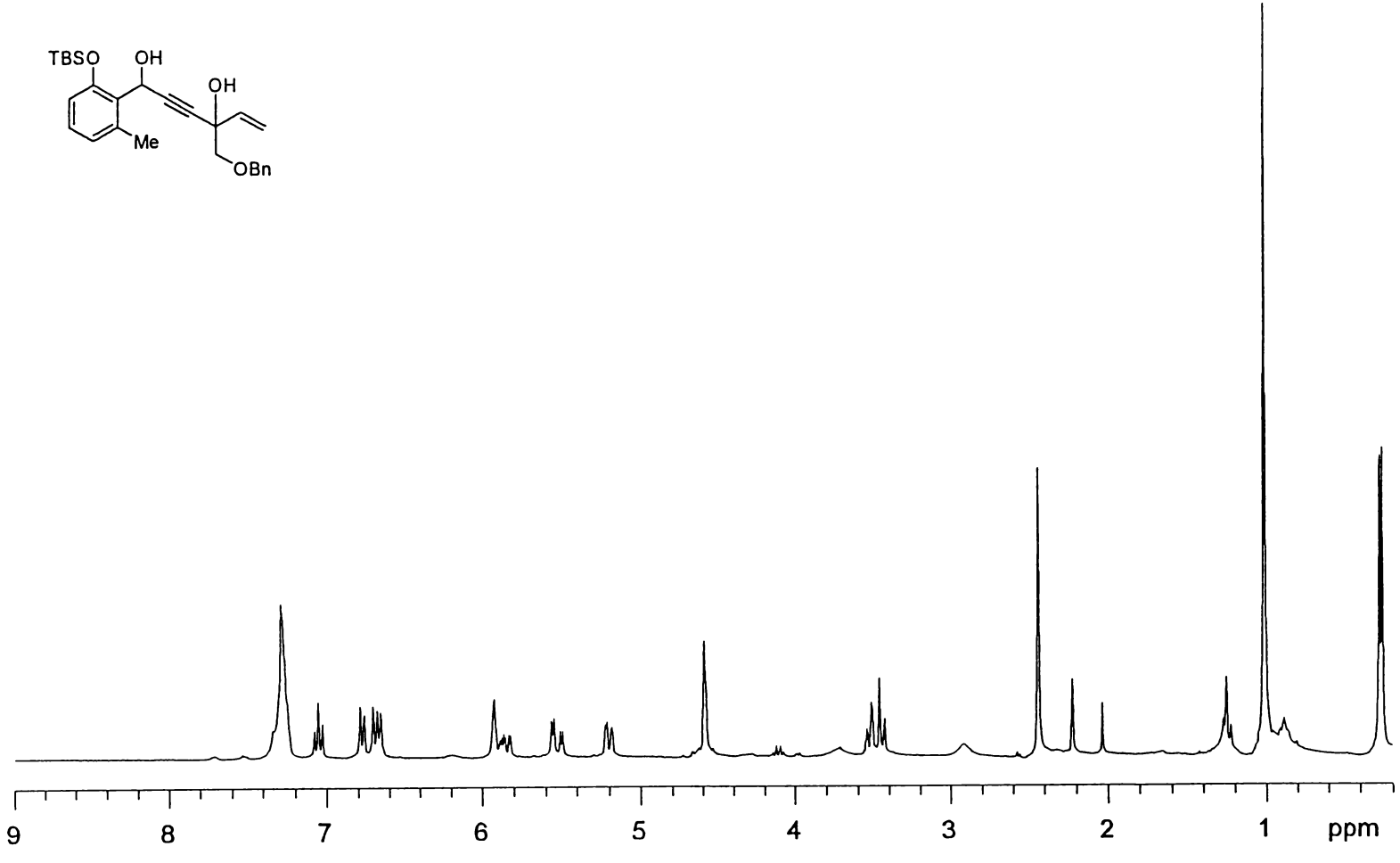
^{13}C NMR Spectrum (75 MHz, CDCl3) of 1-Benzyloxy-2-oxiranyl-but-3-yn-2-ol (**87**).



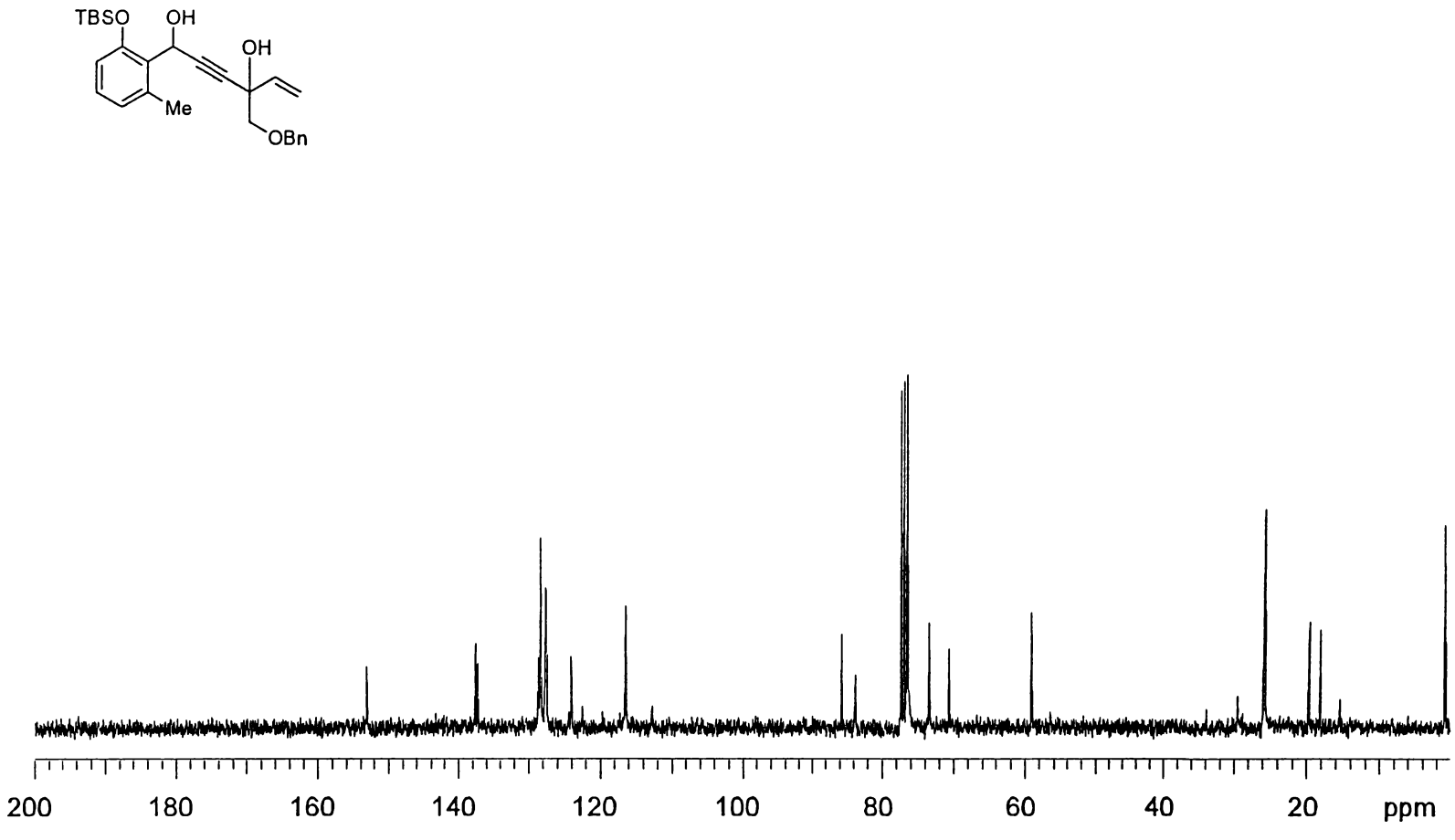
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
1-(2-*tert*-Butyldimethylsilyloxy-6-methylphenyl)-4-methyl-hex-5-en-2-yne-1,4-diol (**82**).



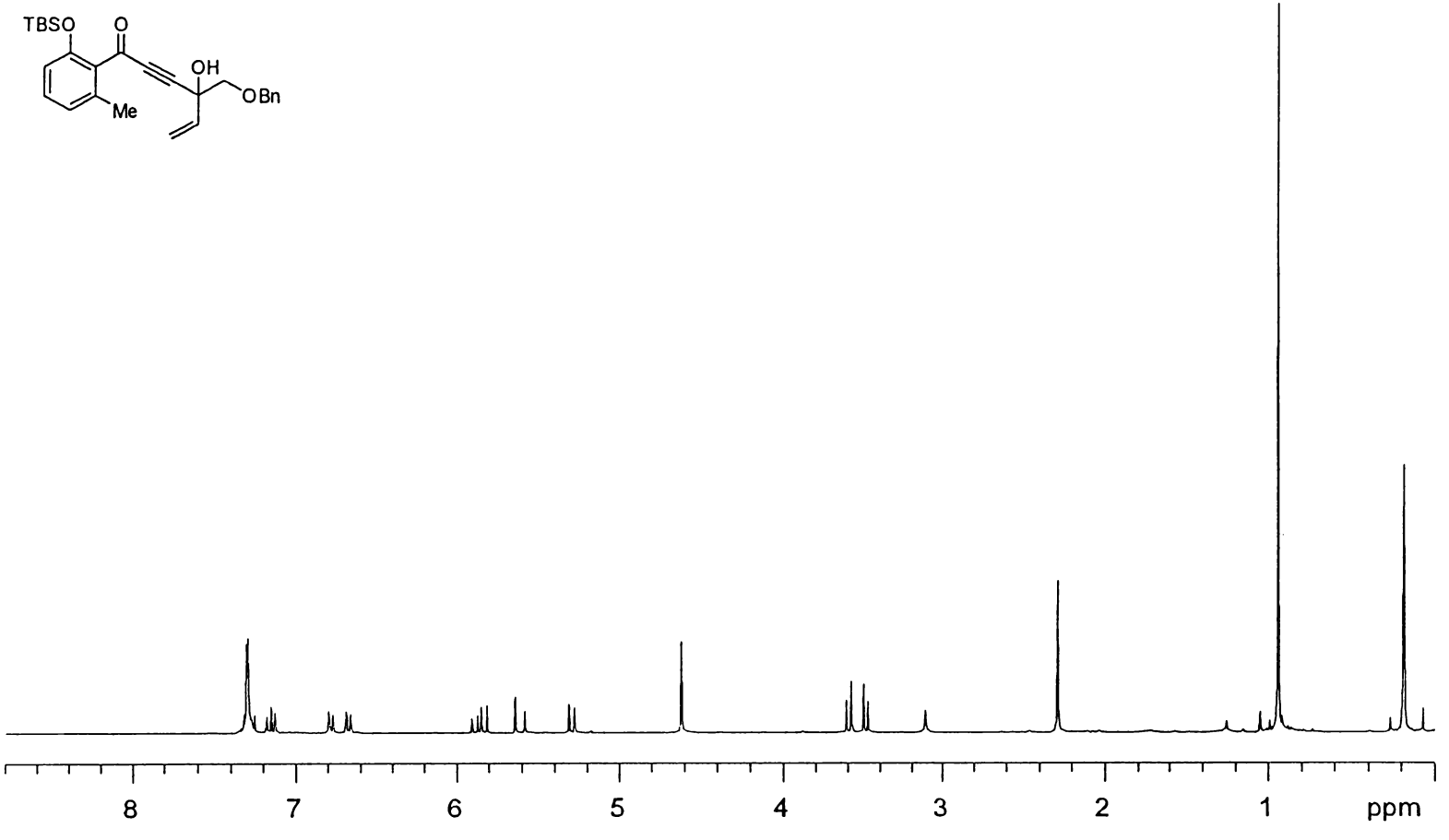
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of
1-(2-*tert*-Butyldimethylsilyloxy-6-methylphenyl)-4-methyl-hex-5-en-2-yne-1,4-diol (**82**).



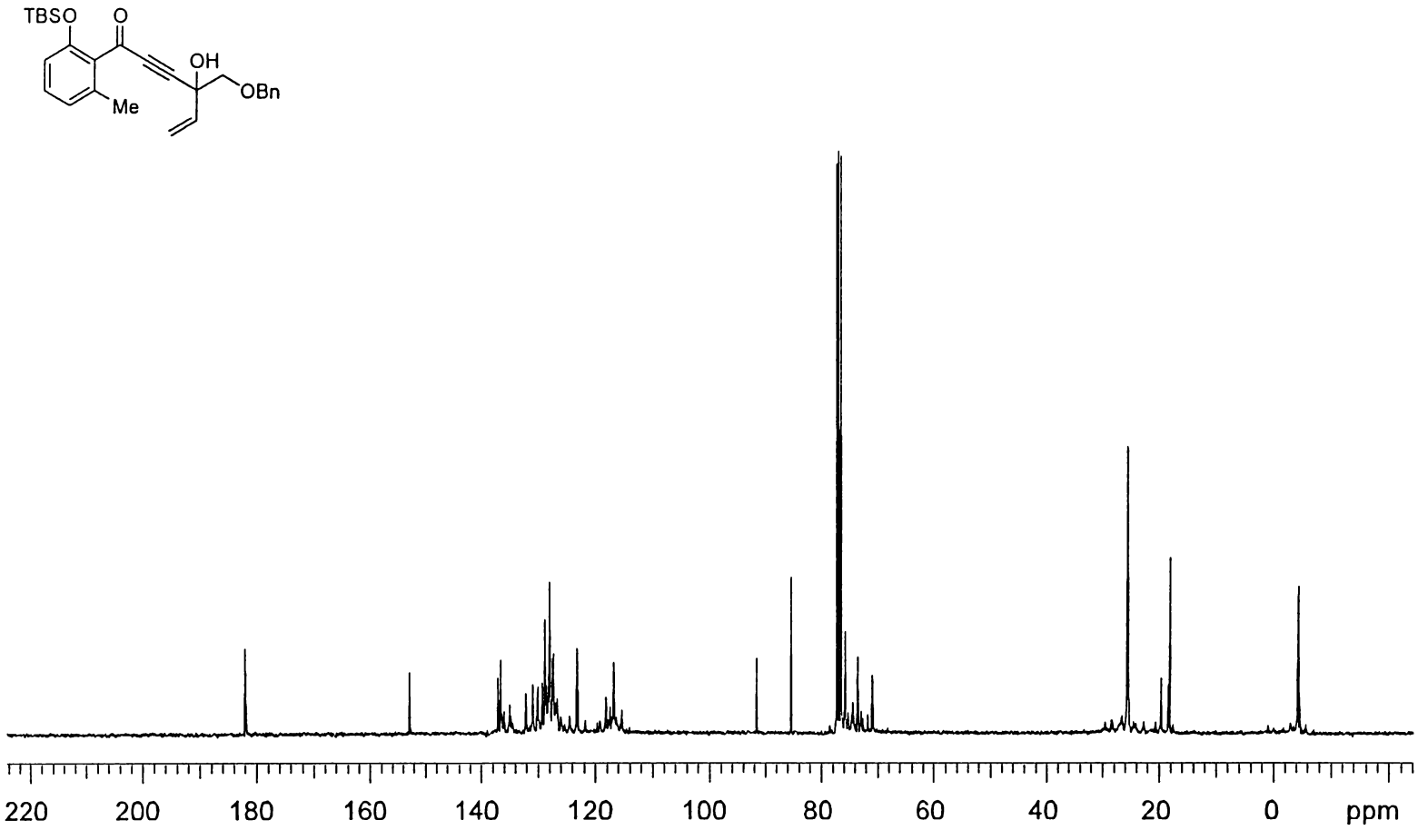
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-hex-5-en-2-yne-1,4-diol (**83**).



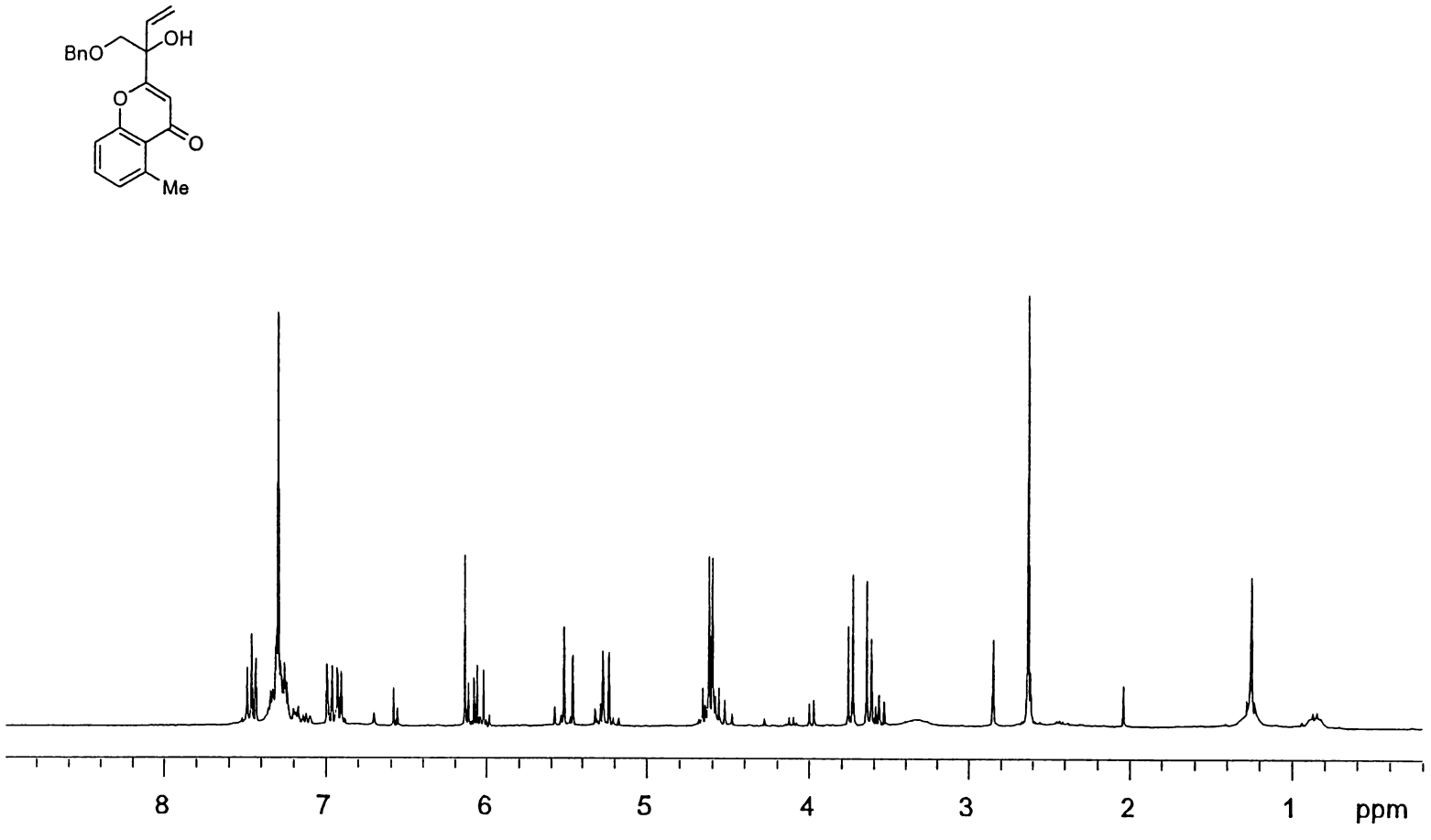
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of
4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-hex-5-en-2-yne-1,4-diol (**83**).



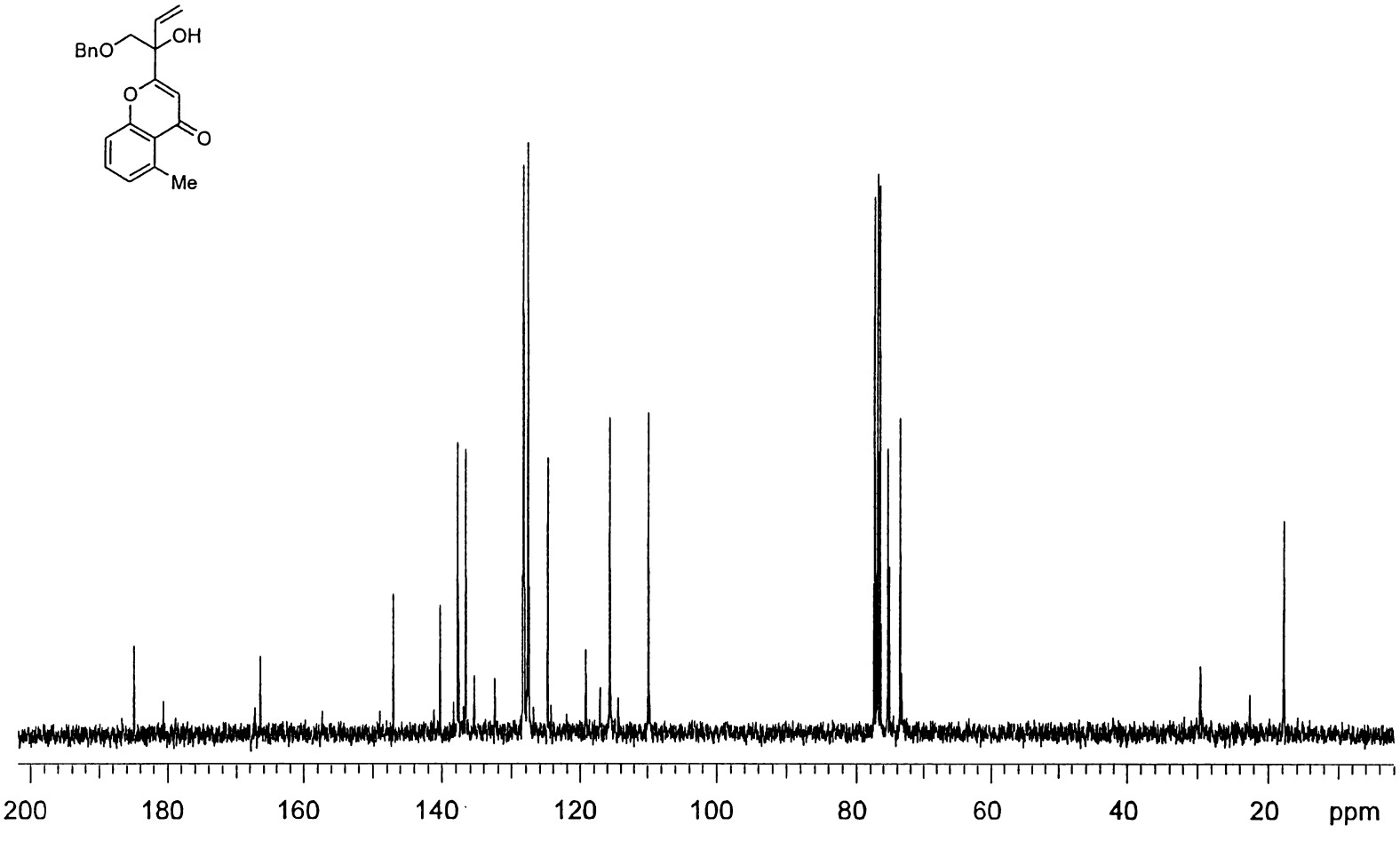
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-4-hydroxy-hex-5-en-2-yn-1-one (**84**).



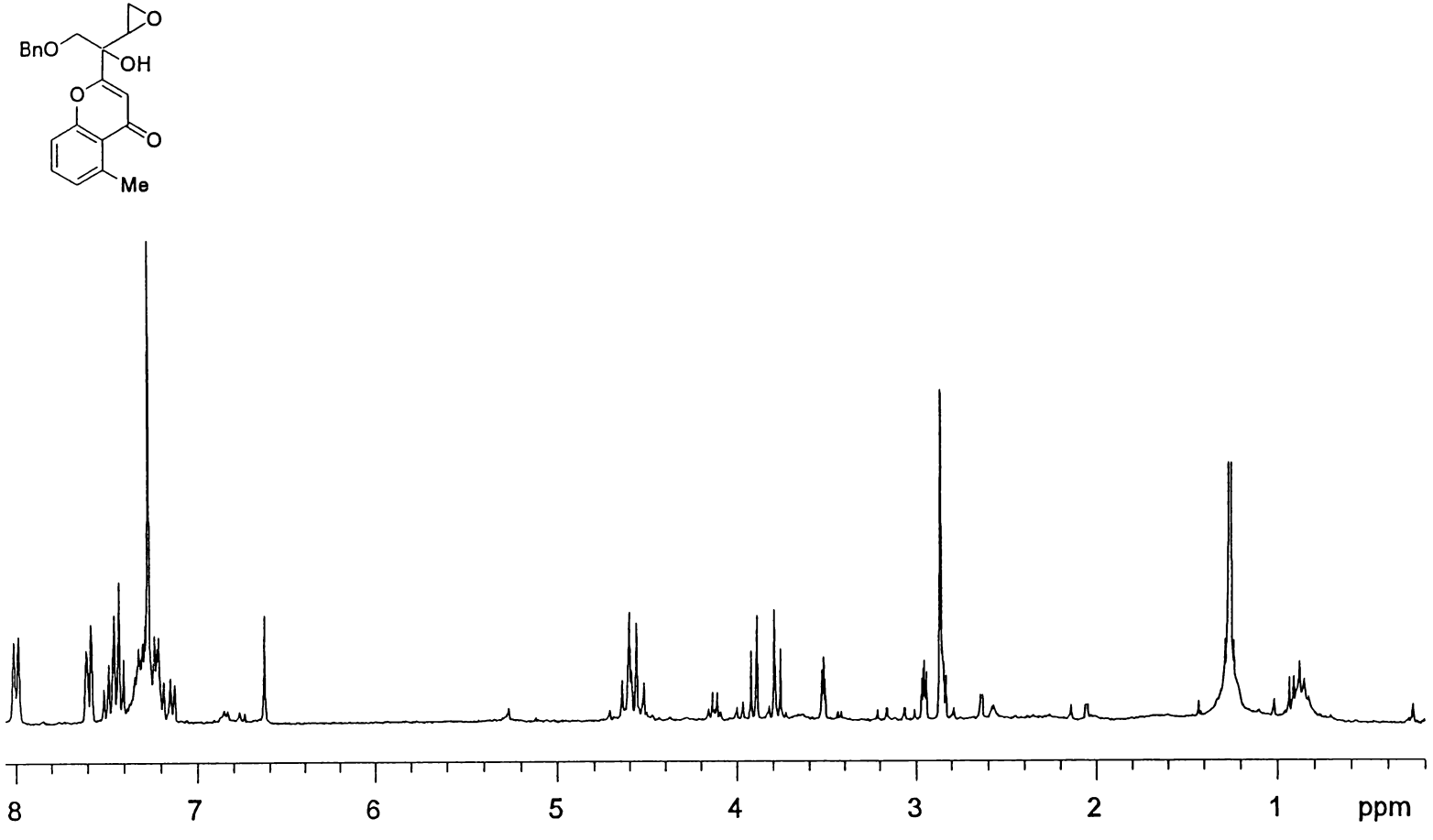
^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of
4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)-6-methylphenyl]-4-hydroxy-hex-5-en-2-yn-1-one (**84**).



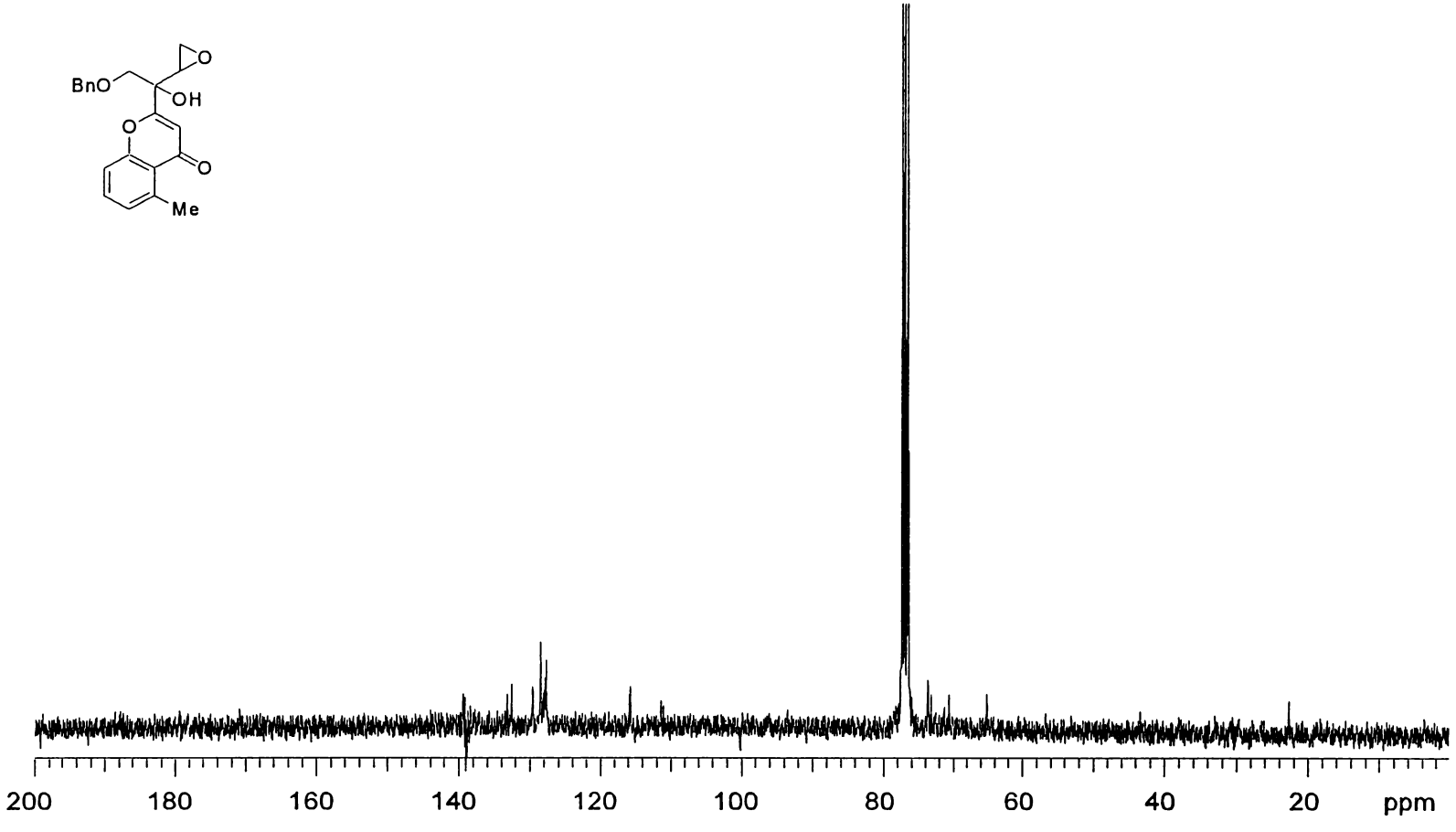
^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of
2-(1-Benzyloxymethyl-1-hydroxyallyl)-5-methylchromen-4-one (**85**).



^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of
2-(1-Benzyloxymethyl-1-hydroxyallyl)-5-methylchromen-4-one (**85**).



^{1}H NMR Spectrum (300 MHz, $CDCl_3$) of 2-(2-Benzyloxy-1-hydroxy-1-oxiranylethyl)-5-methylchromen-4-one (**86**).



^{13}C NMR Spectrum (75 MHz, $CDCl_3$) of 2-(2-Benzyloxy-1-hydroxy-1-oxiranylethyl)-5-methylchromen-4-one (**86**).

VITA

David Charles White was born to Dr. Charles and Mrs. Helen White on March 4, 1972 in Wilmington, Delaware. He attended and graduated, with Honors, from Newark High School, Newark, Delaware in June 1990. He enrolled at Virginia Tech where he achieved his BA (1994) and MS (1997) in chemistry. David was a member of the Virginia Tech Men's Volleyball Team.

In August 1997, David began his graduate studies in organic chemistry at the University of Tennessee under Dr. David C. Baker. During his time at UT, he held graduate teaching and research assistantships for the Department of Chemistry. He was elected to the positions of president of the Association of Chemistry Graduate Students (ACGS) and vice-president of the Younger Chemist Committee (YCC) during his tenure at UT. David was awarded the First–Year Achievement Award in 1998 as well as the Departmental Service Award in both 1999 and 2001. After finishing his cumulative exams, David completed his original research proposal (ORP) in May of 1999. In the Fall of 2001, he completed the requirements for the degree of Doctor of Philosophy in Chemistry. The author is a member of the American Chemical Society and the American Institute of Chemical Engineers.

David has accepted a position at IRIX Pharmaceuticals, Inc. in Florence SC, which he will commence at the conclusion of his doctoral degree. On April 27th of 2002, David will be wed to Ms. Kelly Young of Seymour, TN.